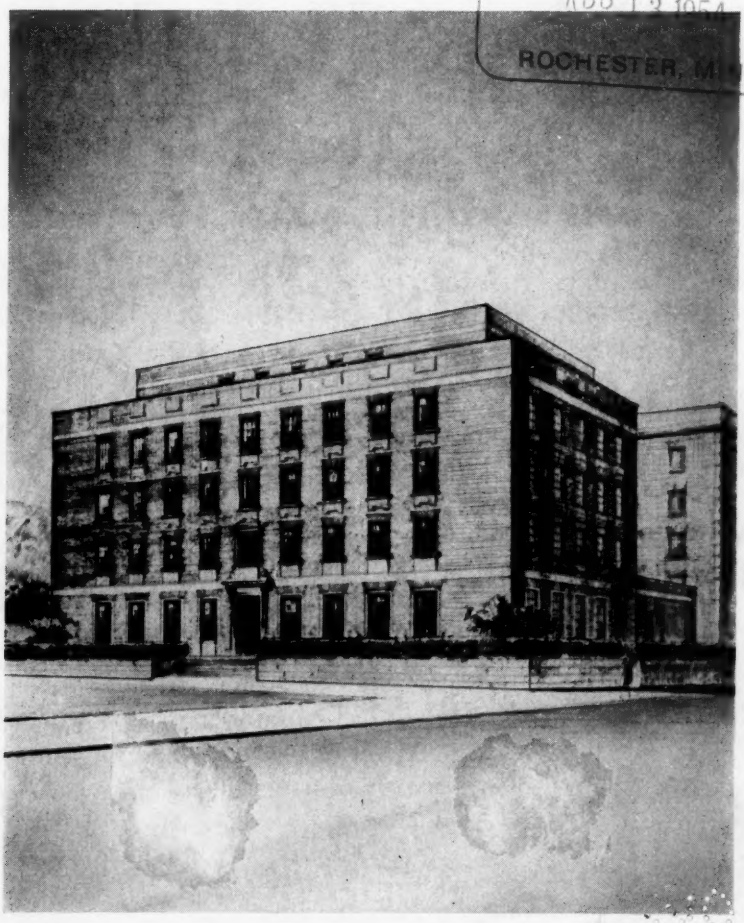
DIABETES

The Journal of the American Diabetes Association



THE CHARLES H. BEST INSTITUTE

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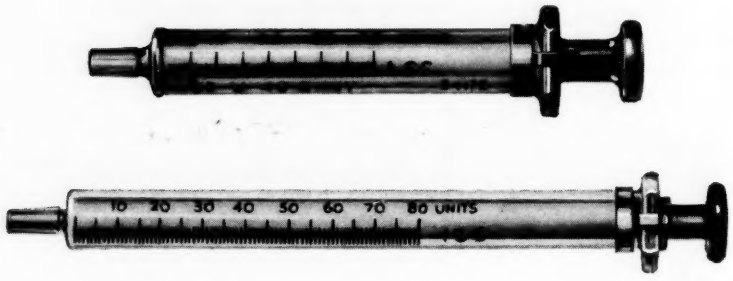

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Carbohydrate Metabolism During Pregnancy

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Translation from the French by

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The relation between carbohydrate metabolism and pregnancy attracted the attention of clinicians and physiologists long before the discovery of insulin[1]. On the one hand, the frequency of a temporary glycosuria in the course of pregnancy led to studies of the carbohydrate metabolism, especially by means of the sugar tolerance test [2, 3, 4]. On the other hand, Carlson and Drennan[5] thought that they had shown support by the fetal pancreas in the course of experimental pancreatic diabetes in the pregnant dog. The discovery of insulin made pregnancy in the diabetic woman an important clinical problem. It led to a remarkable improvement in the outlook for the mother but even so there were difficulties in fetal survival[6, 7]. In spite of insulin treatment fetal death *in utero* or prenatal mortality have remained threatening. Furthermore, this elevated fetal loss rate is established many years before the appearance of clinically apparent, permanent diabetes[8, 9]. Children born of diabetic mothers present obvious characteristics of which the increased birth weight and an increase in the number and size of the islands of Langerhans are the best known[10, 11, 12]. To these observations on the development of children of diabetic or pre-diabetic mothers, may be added the problem of children of diabetic fathers.

In the first part of this presentation, I shall review the most important features in man, namely: 1. The loss of carbohydrate tolerance and the glycosurias of pregnancy. 2. The fetus or newborn of diabetic or prediabetic mothers with practical directions for avoiding the prediabetic infant mortality. 3. The pancreas of gestation. 4. The hypercorticism of pregnancy. 5. The functional relationship between the pancreatic islets and the adrenal cortex in man. In a second, or experimental, part, I shall discuss: 1. Pregnancy in the animal which has its pancreas damaged by alloxan. 2. The abortifacient action of cortisone. 3. The influence of cortisone on placental glycogen. I shall conclude with applications based on the present state of knowledge.

REVIEW

1. *The Loss of Carbohydrate Tolerance and the Glycosurias of Pregnancy.*

The curve of the tolerance test may remain normal throughout the three trimesters of pregnancy in healthy women. According to the observations of Labbe

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and Chevki[2], Allen[3] and Hurwitz and Jensen[4], (see Figure 1), all degrees of disturbance in carbohydrate regulation can appear in one or the other trimester of

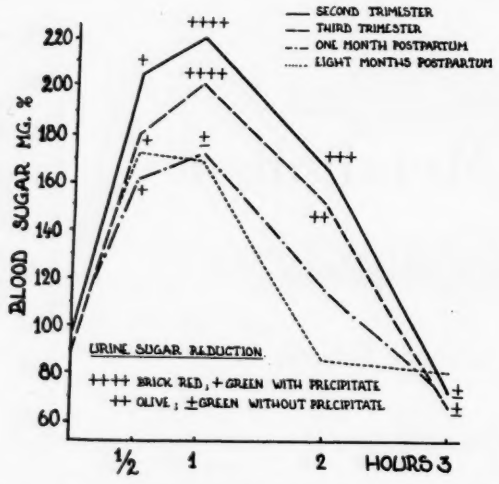

FIGURE 1. Glucose tolerance tests on a patient at various times during pregnancy and after delivery. Note the association of marked glycosuria with hyperglycemia. From Hurwitz, D, and Jensen, New England J. Med., 234, 10:327-29.

pregnancy but disturbances occur most frequently in the last two trimesters[13, 14]. In the course of tolerance tests with 100 gm. of glucose, Frank and Nothman found glycosuria in 100 per cent of their patients. When there is any disorder of the tolerance before pregnancy, the difficulty is exaggerated in the second trimester of gestation but in most cases this accentuated trouble ceases after delivery. The loss of tolerance in these cases recurs in successive pregnancies[15]. It appears that the transitory diabetes which occurs at each pregnancy is transformed by such repetition into permanent diabetes. One usually observes in patients with diabetes of moderate severity that the tolerance to insulin is increased. Thus, in the patient of Verhagen and Byvoet[16], a dose of 90 units of insulin was tolerated during pregnancy. At the end of pregnancy, the blood sugar became normal and insulin could be discontinued completely.

It seems evident that pregnancy constitutes a functional burden on the islands of Langerhans and on the production of insulin[17]. In families with a diabetic trait, or in pre-diabetic women, the disordered carbohydrate metabolism of pregnancy will be clearly characterized many years before the appearance of permanent and clinically recognized diabetes. To give a clear idea of the reality of this transitory diabetes of pregnancy, I wish to cite an especially instructive case described in John's paper on pre-diabetics (Figure 2). In 1934, a 13 year old girl had pruritus and glycosuria for 6 months. On October 30, 1934, a sugar tolerance test was frankly diabetic. Put on a diet, without insulin, she enjoyed good health with no symptoms. The blood sugar was normal during the year 1935; it was often abnormally low (50 to 60 mg. per 100 ml.). In 1938, the blood sugar levels were normal. In April 1944, at the time of a miscarriage, she had a blood sugar of 300 mg. per 100 ml., and 80 units of insulin daily were required to regulate her diabetes. She remained diabetic and in 1948 developed a severe retinopathy, 14 years after the discovery of the transitory diabetes. This case is especially significant, since the patient was thin, and the clarity of clinical observation was not obscured by over-feeding and obesity.

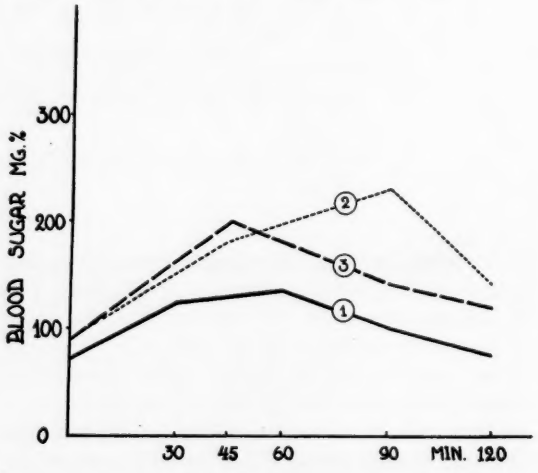

FIGURE 2. Glucose tolerance tests during and after pregnancy, in the case of a woman, aged 38 years, weighing 56 kg. Paternal aunt, diabetic. First pregnancy ended after 37 weeks by cesarean section performed because of severe toxemia; female baby born alive weighing 1.4 kg. Test 1 at eighth week of pregnancy; normal blood sugar curve even lower than average. Test 2 at 24th week; abnormally high blood sugar curve with glycosuria. Cesarean section at 35th week; female baby weighing 2.8 kg. alive. Test 3 one month after cesarean section. Insulin given during the second pregnancy in doses progressively increased up to 30 units twice daily at the end of pregnancy. After the cesarean section, insulin dosage reduced to 5 units daily. The experience of this patient illustrates the fact that glucose tolerance tests may become abnormal in late pregnancy even when normal during the first twelve weeks.

Here pregnancy was not a tolerance test; it was the diabetogenic factor leading to a permanent, "metagestational," diabetes. Lastly, Pompen's[20] case may be mentioned. This case illustrates the hyperglycemic role of pregnancy in a woman who before pregnancy had hypo-

glycemia due to an islet cell adenoma (see also Katsch[17]). Munro and his associates[20] have established the fact that the functional strain on insulin production during repeated pregnancies may lead at last to permanent diabetes when the diabetic diathesis runs in the family, or even in people in whom the inheritance of diabetes is not manifest clinically. Since 1930, anatomical studies permit one to recognize in the histological structure the adaptation of the islands of Langerhans to this increased need for insulin in the course of gestation. I shall summarize in a later section these interesting observations which have been made not only in laboratory animals but in the pregnant woman.

2. *Fetus or Newborn of Diabetic or Pre-diabetic Mothers.*

The transitory hyperglycemias of pregnancy are evidence of insufficient hormonal adaptation to the developmental needs of the uterine content. Clinical observations show that the evolution of these pregnancies leads to a serious fetal loss rate without the clinical recognition of pre-diabetes. Emphasis should be placed on the importance of disorders of carbohydrate metabolism, even of the type called benign, in the pathology of gestation. Many pregnancies are spontaneously interrupted at the third month. There is no good clinical documentation of these miscarriages, but as they appear in the histories of pre-diabetic patients, disordered carbohydrate metabolism appears to play an important role.

The family tree of one of our patients (Figure 3) shows that the first phase of diabetes is manifest at the onset of pregnancy. Four out of 5 pregnancies ended in premature delivery or neonatal mortality. It is only now, that diabetes of an essentially benign type has been recognized. It seems certain that the study of the glucose tolerance in the course of the earlier pregnancies would have led to the discovery of disturbed carbohydrate regulation.

The intra-uterine mortality up to the end of the eighth month of gestation and the neonatal mortality are much easier to relate to pre-diabetes in the mother. In fact, these children show an exaggerated development, their weight exceeds the average, their nutrition is "plethoric" to the point of recalling the facies of Cushing's syndrome. They often die a few hours or days after birth[21–23]. To illustrate this fact, two typical observations are presented. These provide evidence of the correction by insulin of the disordered maternal environment and its role in the survival of the newborn (Figures 4 and 5). One can conclude that control of hyperglycemia and the disturbed glucose regulation of the pre-diabetic pregnancy, is effective in prevention of diabetic embryopathy. Pedersen[24] has offered evidence that maternal hyperglycemia plays a part in the pathology of the newborn of the diabetic mother even when insulin treatment is used.

The prevention of the fetal mortality of pre-diabetic

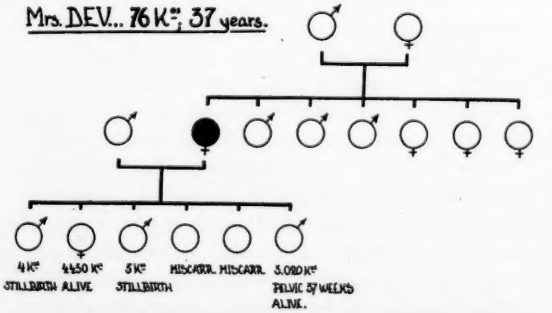

FIGURE 3. Family tree of Mrs. De V. (indicated by black circle) found to have glycosuria after her fifth pregnancy, treated regularly with injections of insulin. Insulin given during the sixth pregnancy: 24 units daily from the sixth to the 30th week; 36 units during the last seven weeks, ten units during the post partum period. Baby born at 37 weeks by natural delivery, weighing 3.02 kg.

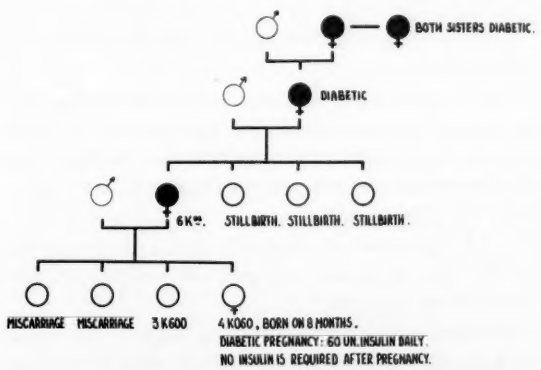

FIGURE 4. Family tree of Mrs. C. (indicated by black circle, lower left) Mother, grandmother, and great aunt, diabetic. Her mother was overweight and died at the age of 40 from an operation for ovarian cyst; three other pregnancies terminated by still birth, each baby weighing more than 4 kg. Mrs. C's first two pregnancies terminated by miscarriage at 5 and 6½ months; fetuses were heavy. Mrs. C then gained in weight to 140 kg. In third pregnancy, female baby born at term, alive, weighing 3.6 kg. In fourth pregnancy, glucose tolerance test at the 16th week showed blood sugars before and at 45 min. intervals after 50 gm. of glucose: 145; 190; 215 mg. per 100 ml. with 2.7 per cent sugar in the urine. Insulin given during the last pregnancy in a dose of 30 units twice daily from the 18th week until after delivery. Female baby weighing 4.6 kg. born after 36 weeks by natural delivery.

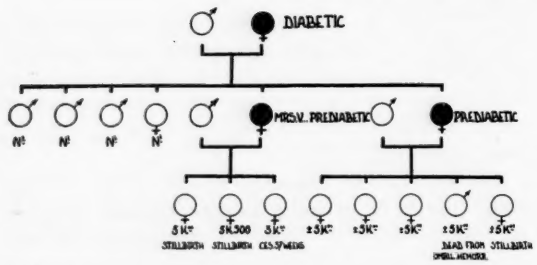

FIGURE 5. Family history of Mrs. V. (age 41, wt. 74.5 kg.) whose mother became diabetic at age 65 and whose sister showed permanent glycosuria following her last pregnancy. In Mrs. V's last pregnancy a glucose tolerance test at the 28th week showed blood sugars before and at 45 min. intervals after 50 gm. of glucose: 99; 202; 180; 153; 112 with 3.4 per cent sugar in the urine after 90 minutes; insulin given 15 units twice daily from the 28th to the 37th week. Cesarean section performed after 37 weeks. Baby weight was 3 kg.

mothers seems to be closely related to the prenatal prevention of the hyperplasia of the islets in the course of embryogenesis. Of course, the functional capacity of this pancreas, which is limited by heredity, will not disappear, but one can protect it against the physiologically stressful circumstances which act from the moment of conception.

Practical directions for avoiding the pre-diabetic infant mortality.

To conclude this outline which summarizes our knowledge and which traces the meaning of our observations for the future, one may formulate practical conclusions which are required of those who are responsible for prenatal advice.

a. All glycosuria of pregnancy should be interpreted in the light of glucose tolerance tests repeated in each trimester of pregnancy.

b. Such tolerance tests should be made in the course of pregnancy when there are diabetic relatives or when a pregnant woman gives a history of abortions, stillbirths or large babies. If the woman herself weighed more than 4.5 kg. at birth, the same care would be taken.

c. The tolerance test performed postpartum or apart from pregnancy throws light on the pathogenesis only if it is abnormal. It may appear quite abnormal from the beginning of the fourth month of pregnancy even if it was normal when the patient was not pregnant.

d. Insulin in the largest doses tolerated and the interruption of pregnancy at about the 35th week are useful for the protection of the pancreatic functions of the mother and of the embryonic nutrition.

One may hope that insulin treatment of every disorder of carbohydrate metabolism occurring during pregnancy may prevent the prediabetic embryopathy and especially the hyperplasia of the islets in the newborn. Extending our hopes still farther, one may anticipate that the pancreas which has been protected during its embryonic development may no longer succumb during childhood to diabetogenic hormonal influences, that is, that a more or less effective prophylaxis of juvenile diabetes could be studied. In any case, one finds here a reason for undertaking the best, practically obtainable, control of every dysfunction of glucose utilization throughout the entire day and throughout the entire course of pregnancy. The prime importance of this objective is presented by Lawrence and Oakley[25] and Peel and Oakley[26], when they compare the survival of infants born elsewhere with the survival of offspring of diabetic mothers receiving medical and obstetrical care at the Kings College Hospital, in which 59 to 75 per cent of the children are saved.

3. The Pancreas of Gestation.

The adaptation of the endocrine function of the pancreas to the burden of gestation has been the object of fruitful research. Numerous investigators[27–34] have described the increased number of the islands, and, still more clearly, the appearance of peculiarly hyperplastic islands of Langerhans.

In the guinea pig the islets are more abundant during gestation than in the non-pregnant female. The islets reach their maximum at the time of delivery. This hyperplasia is manifested only from the 15th day of gestation (at the same time as the release of thyroid activity). The hypertrophy of the islets is particularly striking in pregnant mice and rats. These histological phenomena regress promptly after the birth of the litter. Even a few hours later, the islets are less well stained. The changes have vanished at the end of 4 days.

In women, Rosenloecher[27] observed a striking increase in the shape and number of the islets during pregnancy. He noted particularly that the strands of cells are surrounded by an irregular network of connective fibers and capillaries which disappear in the course of the puerperium. In the normal physiology of pregnancy, the hyperplasia of the islands prevents the disturbing influence of hyperglycemic factors, but in gravid women suffering from functional insufficiency of the

islets will permit hyperglycemia to appear; the loss of carbohydrate tolerance will be easily recognized by a sugar tolerance test.

Among the hormonal factors which are involved in the production of this hyperglycemia, the hypercorticism of pregnancy is the most obvious. One can also note the already numerous studies on growth hormone and its eventual part in the course of pregnancy. But Young[35] observed that the diabetogenic action of growth hormone is lacking during pregnancy. Barns and his associates[36] reported an unfavorable effect of growth hormone on the progress of gestation in the rat. Whatever may be the mechanism of its action, pregnancy is characterized by an appreciable increase in the excretion of adrenal cortical steroids or their end products.

4. The Hypercorticism of Pregnancy.

Since the investigations of Venning and Browne[37, 38], hypercorticism in pregnancy has been demonstrated by both bioassay and chemical methods. Determinations which have been made on blood and urine by many workers[39–44] have shown the quantitative importance of this increased secretion of glucocorticoids. In particular, beginning at the sixth month of pregnancy, the excretion reaches sharply elevated values. At the end of pregnancy and even a few days before the predicted date of delivery, there is a fall in the excretion of glucocorticoids. Bush[42] succeeded in measuring 17-hydroxycorticosteroids in the peripheral blood, although in normal persons the amount is too small to measure. In patients with Cushing's syndrome or even in pregnant patients, the values obtained are instructive:

Table 1

17-hydroxycorticoids in the blood

Patient	(mg. per 100 ml.)
M. at 8th month of pregnancy	13.4
M.K.—Toxemia of pregnancy (39 hours after delivery)	1.7
J.—Toxemia of pregnancy at 37th week	23.0
F.B.—Cushing's syndrome	20.0
B.C.—Cushing's syndrome	11.0
C.—Cushing's syndrome	23.0

Gray[39] showed that the excretion of glucocorticoids is not quantitatively different during the pregnancies of diabetic and non-diabetic women. However, it is not certain that the amount excreted is a true image of the amount of adrenal cortical hormones secreted. Gemzell[45] found that the amount of 17-hydroxycorticosteroids in the blood increases progressively in the course of gestation and falls to the normal level by the 6th day after delivery.

5. The Functional Relationship between the Pancreatic Islets and the Adrenal Cortex in Man.

Studies on animals have led to the establishment of the important relations between the function of the islands of Langerhans and the adrenal cortical hormones since the observations of Long and Lukens[46, 47]. Since then, pathology has furnished various demonstrations of failure of this equilibrium. In particular, when the production of insulin is no longer adequate, when these situations may be classified as pre-diabetes or beginning diabetes, corticotropin or cortisone causes considerable increase in the level of blood glucose and the sugar tolerance curve becomes abnormal. Normally, the capacity of the pancreatic islets to adapt prevents the response to the cortical hormones from being seen in the blood sugar. After bilateral adrenalectomy, the dose of adrenal cortical hormones determines the need for insulin; there is a direct relation between the dose of cortical extract and the dose of insulin which is required and tolerated. Hypercorticism is an important element in insulin resistance[48].

One may consider that the increased need for insulin, provoked by the hypercorticism, throughout the course of pregnancy, places a strain on the functional capacity of the islands. In the first place, this phenomenon explains the increased need for insulin in 70 per cent of pregnant diabetic women[14]. The temporary disappearance of hypoglycemia in the course of pregnancy in women with islet cell adenomas is another manifestation. In the second place, pregnancies amount to a tolerance test; hence the numerous examples of transitory hyperglycemia during pregnancy with the serious effects on placenta and fetus.

6. Other Hormones.

It seems certain that the overactivity of the anterior pituitary and of growth hormone play an important part in pregnancy. In fact, Young[35] observed a striking resistance of pregnant animals to the diabetogenic action of growth hormone. Miller[49] reported the resistance of pregnant animals to diabetogenic doses of alloxan. Reid[50] emphasized the synergism between growth hormone and corticotropin. Moreover, Houssay's[51] studies on the action of sex hormones on experimental diabetes show that the effects of the various hormones must be integrated in a new equilibrium in the course of pregnancy. It is certain that the pancreas which is marred by an hereditary functional deficiency is subjected to a load capable of bringing on a temporary

insufficiency. By the duration, the repetition and the intensity of these periods of hypercorticism which characterize pregnancy, the pancreas will ultimately be brought to permanent insufficiency[52]. The situation then becomes a "metagestational" diabetes, the clinical appearance of which may be hastened by infections, overeating and a sedentary life.

EXPERIMENTAL STUDIES ON DIABETES AND PREGNANCY

Further light may be thrown on the clinical problems raised by the diabetogenic action of pregnancy and the diabetic embryopathy as a result of studies on the pregnant rabbit. The principal results are reported under three headings: a. Pregnancy in the alloxanized rabbit. b. The abortifacient action of cortisone or corticotropin and the disordered carbohydrate metabolism induced by these hormones and c. The effects of cortisone on placental glycogen.

1. Pregnancy in the Alloxanized Rabbit.

In the normal rabbit, pregnancy is attended by only a slight loss in dextrose tolerance. To study this, the blood sugar curve has been followed after the intravenous injection of 1 gm. of glucose per kg., in the non-pregnant female rabbit (Figure 6; Hoet[53]).

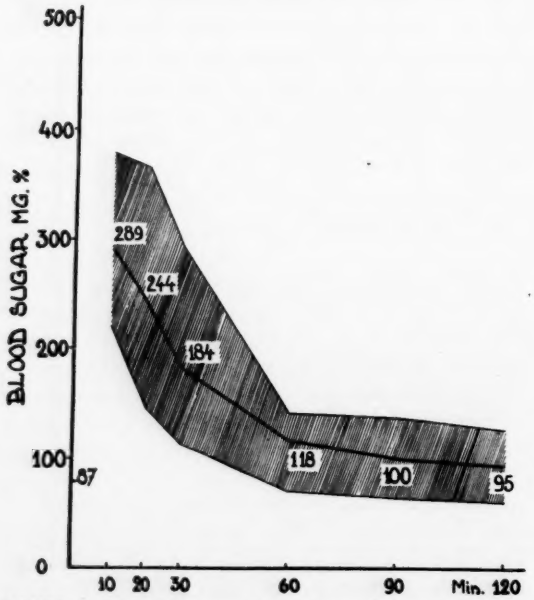

FIGURE 6. Glucose tolerance tests in normal non-pregnant female rabbits by intravenous injection of 1 gm. of glucose per kg. of body weight, average of 50 tests.

One can attribute the fact that the glucose tolerance test does not become more abnormal during pregnancy to the faculty for adaptation of the islands (well shown by anatomists in the pancreas of pregnancy). On the contrary, when the pancreas is artificially weakened by a subdiabetogenic dose of alloxan (75 mg. per kg.), a dose which by itself leads after 6 to 7 days to no modification of the sugar tolerance, pregnancy becomes a frankly diabetogenic event. Figure 7 shows an experiment of this kind. All these experiments have confirmed the observations of Miller[49] and others [54 and 55] showing that in the previously alloxanized rabbit, premature resorption of the fetuses occurs.

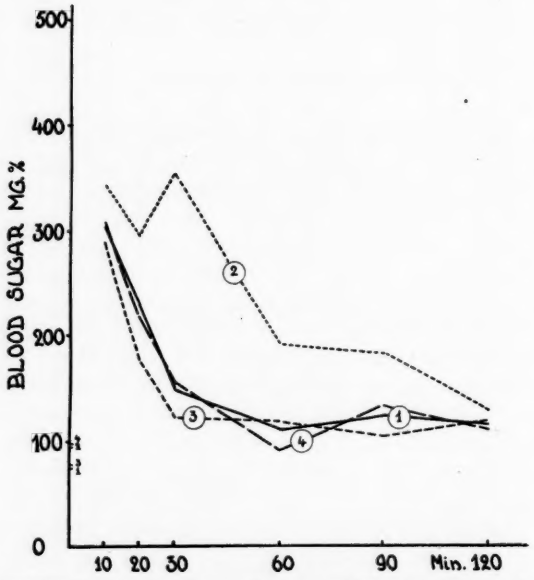

FIGURE 7. Glucose tolerance tests on rabbits given 75 mg. of alloxan per kg. of body weight daily for 6 to 7 days, then impregnated on the 9th day. Test 1 on first day of pregnancy; Test 2 on 15th day of pregnancy (resorption occurred afterwards); Test 3 on 20th day (after resorption); Test 4 on 25th day.

Bartelheimer and Kloos[56] have described the harmful influence of an established alloxan diabetes in the pregnant rat. When rats could survive, they presented gigantism; some of them even became frankly hyperglycemic at the age of 3 or 4 months. Hultquist[57] described the changes in rats which had been born of depancreatized rats. These newborn are often unduly heavy and have hyperplasia of the islands of Langerhans.

These experimental findings agree with the clinical observations of several authors[11, 12, 14, 58] concerning the hyperplasia of islet tissue which is seen in the infants of diabetic mothers. They also enlighten the

obscure problem of the abnormal fetal mortality and the large infants which are typical of the prediabetic period.

In rabbits in which the blood sugar has again become normal after the administration of a small dose of alloxan (75 mg. per kg.), pregnancy leads to a transitory loss of tolerance, a true diabetes of pregnancy. However, in spite of the fact that the diabetes is temporary, it has the same harmful effects on the fetus and on the newborn[59].

2. *The Abortifacient Action of Cortisone or Corticotropin and the Disordered Regulation of Carbohydrate.*

Courrier and Cologne[60] and Robson and Sharaf[61] noted the abortive action of large doses of cortisone. This steroid has even been suspected of having a progestational effect[62]. The studies of P. L. Hoet[53] and Brasseur[59] have shown that the disorder of carbohydrate regulation caused by adrenocortical hormones plays an important causative part in their abortive property. In a dose of 2 to 5 mg. per kg., beginning at the 12th day of gestation, corticotropin is harmful to the rabbit's embryo. At a dose of 2 mg., the pregnancy can go to term, but the fetuses are dead, small in size and often macerated. On the other hand, at a 5 mg. dose, the pregnancy never goes to term and there is always resorption between the 17th and the 24th day.

Cortisone regularly causes the interruption of pregnancy by abortion or resorption when doses exceeding 2 mg. per kilo daily are administered from the 12th day of gestation. As with corticotropin, the interruption of gestation is even more rapid as the dose of cortisone is increased. For example, if one gives 2 mg. per kg. of cortisone daily it takes 13 days, whereas when 5 mg. are given, it takes 9 days and for 10 mg. only 5 days to interrupt pregnancy. With hydrocortisone, 7 days of treatment at the 2 mg. level suffice to halt embryonic development. Thus, if one compares them at the same 2 mg. dose, 13 days are needed with cortisone and only 7 days with hydrocortisone to obtain the termination of pregnancy. The 2 mg. dose of hydrocortisone is almost as active as the 5 mg. dose of cortisone in the interruption of pregnancy.

Now, if one examines the carbohydrate regulation in pregnant rabbits treated with corticotropin, cortisone or hydrocortisone, one finds that the diabetogenic effect of these agents is striking, constant and more or less proportional to the dose administered (Figure 8, 9, 10). In contrast to this, non-pregnant control rabbits, which were given the same doses of these hormones for the

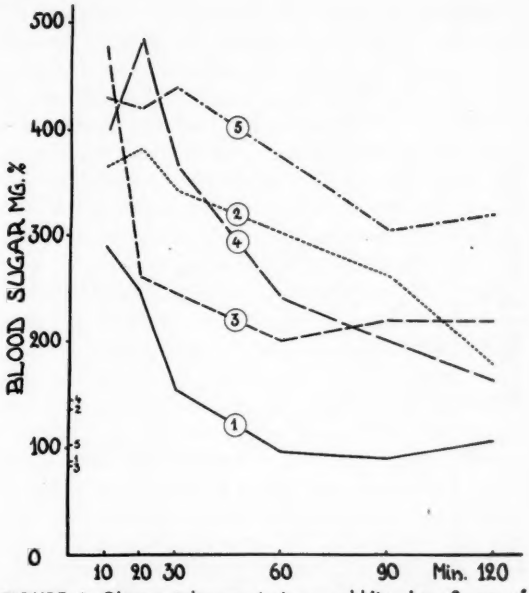

FIGURE 8. Glucose tolerance tests on rabbits given 2 mg. of corticotropin per kg. of body weight daily from the 12th day of pregnancy. Test 1 before pregnancy; Test 2 on the 15th day of pregnancy; Test 3 on the 20th day of pregnancy; Test 4 on the 25th day of pregnancy; Test 5 on the 29th day. (Two very small dead fetuses were born on the 28th day.)

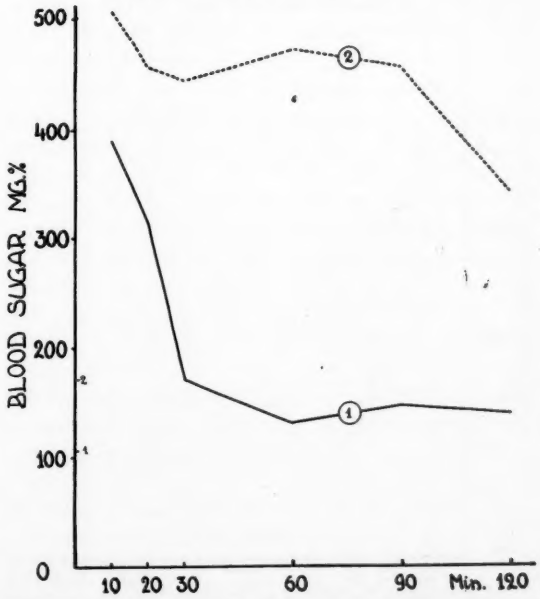

FIGURE 9. Glucose tolerance tests on a rabbit given 10 mg. of cortisone per kg. of body weight daily from the 12th day of pregnancy. Test 1 before pregnancy; Test 2 on the 14th day of pregnancy when 7 dead fetuses were born.

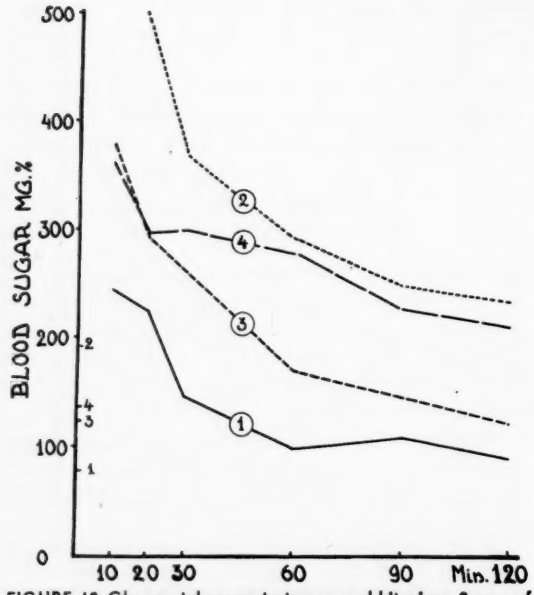

FIGURE 10. Glucose tolerance tests on a rabbit given 2 mg. of hydrocortisone per kg. of body weight daily on the fourth day of pregnancy. Test 1 before pregnancy; Test 2 on the 15th day of pregnancy; Test 3 on the 18th day (resorption of the fetuses); Test 4 on the 21st day.

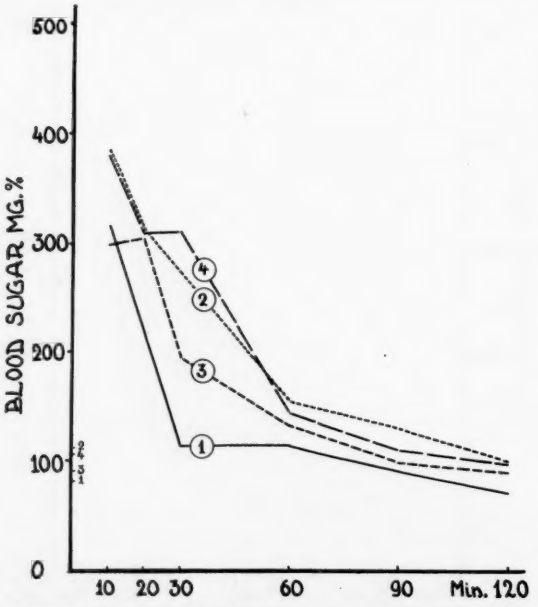

FIGURE 11. Glucose tolerance tests on a non-pregnant rabbit given corticotropin 5 mg. per kg. of body weight daily. Test 1 before corticotropin; Test 2 after 3 days treatment with corticotropin; Test 3 after eight days of treatment; Test 4 after thirteen days of treatment.

same periods, show little or no reduction in their sugar tolerance (Figure 11).

In order to explain the much more marked loss of glucose tolerance in pregnant animals, one must admit that pregnancy is a strain on the islets, making them more sensitive to the diabetogenic action of cortisone or corticotropin.

Moreover, if one compares the tolerance tests of pregnant rabbits treated with 2, 5 or 10 mg. of cortisone and with 2 mg. of hydrocortisone, one finds a striking parallelism between the importance of the disorder of glucose regulation and the speed with which gestation is interrupted: both mechanisms appear closely related[59]. Brasseur[59] has also used sugar tolerance tests to study other endocrine disorders of gestation which in the rabbit lead to the resorption or death of the fetus or the interruption of pregnancy.

In the pregnant rabbit, the daily injection of 1 mg. of estradiol benzoate leads to abortion in 8 to 12 days. No reduction in glucose tolerance could be demonstrated either before or at the moment of the interruption of pregnancy.

The daily administration of the water soluble glucoside of desoxycorticosterone, in dosage of 10 mg. per animal daily, beginning at the 12th day of pregnancy, is fatal for the uterine contents, yet there is no appreciable disorder of glucose metabolism.

Growth hormone (somatotropin) prepared by Wilhelmi's method, in a dosage of 5 mg. per kg. given from the 12th day, leads to fetal death. There was no hyperglycemic tendency in the course of pregnancy. On the contrary, a fall in the fasting blood sugar was noted following the administration of growth hormone.

These observations demonstrate the quite specific role of the glucocorticoids (or corticotropin) in the maintenance of gestation and the regulation of fetal nutrition. In addition, the abortive action of these adrenal hormones must be mediated by the disordered glucose metabolism. The counteracting of this abortive action by treatment with insulin has been examined in recent experiments.

3. *The Effects of Cortisone on Placental Glycogen.*

There seems to be a direct correlation between the role of gestational hypercorticism in the development of the uterine contents and the pathogenesis of the interruption of pregnancy by high doses of adrenocortical hormones.

The experimental exploration of this problem was undertaken in the course of studies on placental gly-

cogen, which are still in progress. Our preliminary results permit a partial interpretation of the relation between the temporary diabetes of pregnancy and the final development of the fetus.

The results of Villee[63] on the metabolism of placental slices *in vitro* also confirm our findings.

Claude Bernard[64], at the time of the discovery of liver glycogen, demonstrated the presence of significant amounts of glycogen in the mammalian placenta, especially in the rabbit.

From the 8th to the 21st day of the gestation, the placenta contains more and more glycogen up to values of 5 per cent. Towards the 21st day, the development of the fetus takes place at a more and more accelerated rate and the placental glycogen tends to diminish until it reaches a value of 1 per cent by the 30th day[65].

P. L. Hoet[53] has investigated the effects of cortisone on the level of placental glycogen in the pregnant rabbit. At the dosage of 2 mg. per kg. or more, which led to the resorption of the fetus, cortisone diminishes glycogen markedly; this is well established for the second half of gestation. The values for placental glycogen in rabbits which had dead fetuses, were between 0.2 and 0.3 per cent (19th day of gestation). This value is very low in comparison to the normal level. In rabbits at the 14th day of gestation and at the lower dose of 0.5 mg. per kg., cortisone increases placental glycogen without interrupting pregnancy. Table 2, Series A, records the results of these experiments. The reported values are based on analyses of both portions of the placenta (maternal and fetal). By the 14th day it is possible to separate the fetal from the maternal placenta. In Table 2, the rabbits were killed on the 14th day after having received 4 daily doses of 0.5 mg. of cortisone per kg.

Table 2

Effects of cortisone on placental glycogen

Rabbit No.	Maternal Placenta		Fetal Placenta	
	Controls[1]	0.5 mg./kg of cortisone for 4 days[2]	Controls	0.5 mg./kg of cortisone for 4 days[2]
	Glycogen—per cent		Glycogen—per cent	
A. Treatment from 10th to 14th day of pregnancy				
1	2.01	5.25	—	1.45
2	3.60	5.78	0.52	1.48
3	4.10	6.24	0.64	2.70
4	2.00	4.70	0.64	2.50
5	1.80	4.98	0.57	1.85
B. Treatment from 15th to 19th day of pregnancy				
1	0.87	0.47	0.30	—
2	0.81	0.46	0.25	0.28
			0.32	0.26

[1] Pregnant rabbits which had been mated at the same time as those of the respective series of treated rabbits.

[2] In series A, 5 placentas were taken from each animal; in series B, 3 placentas from each animal.

Treatment with cortisone increased the values for placental glycogen; the increase in the level of the fetal placenta is quite marked. The passage of dextrose into the fetal economy is thus favored by cortisone. One sees here evidence that the hypercortisonism of pregnancy is a significant factor in fetal nutrition. When the injections of cortisone (0.5 mg. per kg.) are given from the 15th to the 19th days, that is to say at the time which marks the beginning of fetal development, cortisone reduces the glycogen values (table 2, series B).

However, in this experiment (series B) the fetal weight showed that at this stage of gestation cortisone activated fetal nutrition. In fact, the control rabbits who were fertilized on the same day as those treated with cortisone, carried 7 fetuses, the mean weight of which was 2.12 gm. The treated rabbits carried 12 fetuses weighing on the average 2.75 gm. This means that the treated animals produced a total fetal weight of 33 gm. against a total fetal weight of 14.84 gm. in the control rabbits. This result gives only one indication: too many uncontrolled factors are involved in fetal nutrition at any given stage of gestation to accept this result as clearly significant.

In view of the clinical observations on the favorable effect of pregnancy in women with Addison's disease, we have repeated the preliminary studies of Houssay[66] on pregnancy in the adrenalectomized rat. He concluded that the newborn of adrenalectomized animals are smaller than normal.

Overbeek[67] has been studying gestation in rats which were adrenalectomized and treated with desoxycorticosterone. In 59 per cent of these adrenalectomized pregnant rats, death occurred during the last days of pregnancy. Of the young rats which were born alive, 70 per cent died during lactation, which means that in spite of desoxycorticosterone, these pregnancies were grossly disturbed. Houssay's observation on the reduction of fetal weight after adrenalectomy has not been confirmed because of the high fetal wastage among adrenalectomized animals.

Our interpretation of the role of the glucocorticoids in pregnancy is still fragmentary. However, it seems certain that the placenta itself could be a source of 17-dehydro-17-hydroxycorticosterone. Traces of 17-hydroxycorticosterone and three other unidentified steroids have likewise been demonstrated[68].

In conclusion, cortisone acts on the level of placental glycogen: by its mediation it favors the passage of dextrose to the fetus. It is logical to conclude that by means of the action of variations in fetal blood sugar, the islands of Langerhans will be affected in various ways and

will undergo such influences that hyperplasia or other forms of anatomical adaptation will result.

SUMMARY

The permanent diabetes which appears in women in the fourth decade is the culmination of multiple harmful events which have damaged the islands. Overeating and obesity have an unfavorable effect. In patients with a diabetic trait or with latent weakness of insulin production, pregnancies provoke a disturbance in the regulation of carbohydrate metabolism, as evidenced by the hyperglycemic tolerance curve. This curve does not become abnormal until after the 4th month of pregnancy and may not be accompanied by glycosuria. This disordered glucose regulation of pregnancy disappears or tends to diminish from the day after delivery.

The consequences to the fetus and newborn are serious. The fetal loss rate progresses from 20 to 50 per cent in proportion to the increasing severity of the disordered glucose metabolism. A large number of the infants who are born alive have an excessive weight of 5 kg. or more.

In the normal pregnant woman, the pancreas adapts itself to the functional demand by hyperplasia of the islets. Among the various endocrine factors, which take part in the maintenance of gestation, the hypercorticism of pregnancy is the one which, according to experimental and clinical studies, is most directly in functional relation with the islets. The hyperglycemic or prediabetic dysfunction provokes hyperplasia of the islands, which is characteristic of infants born of diabetic mothers[58].

The tendency to obesity, hyperglycemia and finally diabetes which characterizes the ultimate development of a great number of these infants are the consequence, on the one hand, of heredity and, on the other hand, of the maternal environment of *milieu interieur* at the time of embryonal development. The correction of these disturbances of carbohydrate metabolism by insulin prevents the fetal loss rate and the infant mortality[69]. One may anticipate that by normalizing the maternal environment, the hyperplasia of the islands will be reduced. The future will show whether the course of events will be more favorable.

Clinical observation is in accord with the experiments of Bartelheimer and Kloos[56] on rats born of alloxan diabetic mothers. The males of such litters exhibit above-average growth. Furthermore, in some of them hyperglycemia up to 300 mg. per 100 ml. appears after 2 or 3 months, with or without glycosuria.

The experimental studies of P. L. Hoet[53] and Brasseur[59] show that the pregnant rabbit is very sensitive to the hyperglycemic action of 11-oxysteroids. The abortive action of glucocorticoids is accompanied by a serious disorder of glucose regulation. In non-abortive doses, the glucocorticoids increase placental glycogen and favor fetal nutrition. These observations allow one to hope that by correcting the transitory hyperglycemia of pregnancy by insulin, the newborn of so-called prediabetic mothers will not only survive but will likewise have normal growth and development.

To recognize prediabetic mothers it is necessary to perform sugar tolerance tests in each trimester of pregnancy, especially in families with the tendency to diabetes.

Observations[70, 71] on the differences between children of diabetic mothers and diabetic fathers point to the causative importance of the maternal environment.

The correction of the temporary hyperglycemia of pregnancy by insulin may prevent the appearance of permanent diabetes in the mother, and the anatomical and functional anomalies due to the diabetic embryopathy in the infants.

The part played by growth hormone, the thyroid hormone, estrogens and gonadotropins deserves further study; this will make it possible to integrate the endocrine disorders of pregnancy into a more complete picture.

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The Essential Factor in Research

. . . One may assume that this great new Institute is wonderfully equipped for the prosecution of research under modern conditions and there can be no doubt that, with the inspiring leadership of its head, it will make outstanding contributions to scientific knowledge.

But it is interesting to inquire which of these two basic factors is the more important. Is it the extensive and spacious provision of modern equipment or is it the inspiration, guidance and urge derived from a leader? . . .

We can, of course, be quite sure that, in early days, neither Charles Best himself nor his colleagues had the facilities which the Professor of Physiology will now command and order, and I sometimes wonder whether with the wealth of equipment which is now available, especially in this hemisphere, and often in commercial houses of great repute, it is not sometimes forgotten how much more important is the human brain than all the elaborate apparatus which modern science requires.

Excerpts from "Some Aspects of a University's Work," an Address Given by Sir Lionel Whitby at the Special Convocation of the University of Toronto on the Occasion of the Opening of The Charles H. Best Institute on September 15, 1953. Can. M. A. J. 70:194-96, February 1954.

Research and Thinking Processes

R. D. Lawrence, M.D., London, England

I am indeed honoured to speak on this very great occasion when a vast drive of energy towards physiological and medical research has just been enshrined in a beautiful and functional new building—The Charles H. Best Institute. Largely I know why I have been asked to speak, a diabetic myself rescued from death by the early researches of Banting and Best and the discovery of insulin, and partly as a representative of the British Diabetic Association and now of the International Diabetes Federation. In their name I offer our homage to this new achievement in Toronto. But what else, I ask myself, have I to say worthy of this occasion. Certainly no important new discoveries in laboratory medicine; no novel clinical facts. But I should like to lead your attention to certain considerations of thinking processes in research which interest me. I have had no systematic education in philosophy and its nomenclature and shall have to try to describe my ideas in the simplest of words.

The first question that interests me is whether there is any difference between common sense and scientific processes of thought and if so what is the difference? I am simple enough to believe there is a common mental process behind all our thinking and I shall try to analyse what this is. I hope you will not find this so elementary as to be unworthy of this great occasion.

When our attention is occupied by a thing or a happening which presents itself to our senses, our minds put it into place, or in other words assess its significance. In this "thought" really asks what are its relationships, what is behind it in the past and may ask what it will lead to in the future. We are observers in the present of an event or happening in time, which commenced in the past before our present awareness of it and leads onwards to a future event which again we may observe later. When we think, our minds ask into what sequence of *cause and effect* does the happening fall, cause being the earlier phase of the effect we observe and this is the essence of thinking processes. If the fact is nothing new and falls into previous experience, it does not occupy our thought for long and is accepted as a readily explained and commonplace sequence of events. Most people receive and accept the fact relationships that constitute common sense thinking not only from their own experience but from the heritage of accepted experience of their parents, their teachers or the social group in which they live. So there is a ready explanation and acceptance of the ordinary facts of life giving rise to little thought. It is only the unusual, the unexplained happening that gives rise to questioning thought and perhaps most minds shun such an enquiring effort into cause and effect sequences. Let us take a simple example of the above processes. Our door opens, we look for the cause of this happening and expect from experience someone to enter. No one does and so we look further for an explanation and find the cause to be a broken latch. This effect in the present will be a cause of draughts in the future. Thus the sequence of cause and effect goes on and we think in no other way than in these time-related sequences—"the way things run." I am not concerned here with the emotional and instinctive feelings which rule our motives, often subconsciously.

The process of learning cause and effect relationships or associations starts early and indeed is the basis of all experience and of education. A child burns its finger in a bright heat and, connecting the two for the first time, learns that flame is the cause and pain the resulting effect. By 5 or 6 years the questioning process is rampant and every new experience in many children leads to an irritating why, why? The puzzle of a lock to a boy, a complicated mechanism to an engineer, an abstruse problem to a mathematician or philosopher, the problems of how nature works to a physiologist or a new drug to a medical scientist, all give rise to the same cause and effect search for a logical explanatory answer. *Post hoc, ergo propter hoc* is the natural trend of all thinking, though this may have its dangers in science from too easily accepting the seemingly obvious. Whether this inevitable process is imposed by the anatomical and physical nature of the human brain I shall not discuss here. So true thinking results in an appreciа-

Presented at the opening of The Charles H. Best Institute in Toronto, September 17, 1953.

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tion of causal relations from a sequence of observed facts and the drawing of a correct inference or conclusion therefrom—"putting two and two together." A true conclusion can be drawn quite correctly from the quite simple observations and experience of everyday life and this is the essence of common sense. And the more a conclusion is checked by non-contradictory observations, the more likely it is to be true. The scientific process of thought does not differ in nature from common sense thinking but science sets itself more complex problems than the simpler ones of everyday life. Experimental physiology and medicine probes into the hidden secrets of nature by increasingly complex techniques and must demand a multiplicity of agreeing measurements and controlled observations before a sequence of cause and effect is accepted as true; before a general law of relationship is established. The difference lies in the rigor of proof required.

A consideration of weather problems may usefully illustrate the above ideas on simple and complex relationships. A Londoner, simple-minded in matters of weather at least, gets out of bed on Bank Holiday, sees clouds in the sky, concludes that it will rain, cancels his outing to the seaside and turns to sleep again—a too simple inference that with clouds it will rain. This contains an element of truth but is founded on only one observation and too little experience of such a complicated matter as the changeable English weather. The shepherd, more experienced in weather, asks himself, is the air cold or warm, is the wind north or south, and from these added observations can usually decide whether his morning clouds mean rain—ordinary common sense thinking. Nowadays the more knowledgeable ask for more facts, the height of the barometer, its rise or its fall, before they draw conclusions. And the weather expert, be he amateur or professional, wants to know the barographs and other indications such as are now published in the newspapers before he forms his opinion. His conclusions are founded on a wide assemblage of factual observations from weather stations and ships widespread over thousands of miles, far outspanning his local observation of clouds and winds, but controlling them. And from years of observation of such facts and analysis of their cause and effect relations, patterns and general laws of weather sequences have been built up by what is called induction into the science of meteorology. Its main laws and generalisations have become relatively simple, the patterns of low and high pressure systems, cyclones and anticyclones, and can be learned in an hour or two by a senior schoolboy. Knowing and applying these general laws, by a process known as *deduction* to our own local observations of the barometer and the direction of the wind, we can make a far more accurate assessment of the weather that immediately concerns us than were we ignorant of these *general* laws. So far the science of meteorology can go: and the above is a general illustration of the methods and purposes of science, to build up from observed relations of facts, general laws and principles. But when we ask for absolute explanatory knowledge of why a low pressure system starts in the West Indies and travels to sweep rain over England from the west or why high pressure systems pile up in Siberia and push a different type of weather over Europe we get no clear answer. There is as yet no *absolute* or fundamental knowledge in the science of meteorology. And this is the point where research steps in to probe into the unknown and to explain it. The same applies to all growing points in every science, in physiology and in medicine. There are some absolutes and ultimates in scientific knowledge but usually they are limited, such as Boyle's Law. More often when we have solved one problem, and this is very true in biology, the answer only leads to other questions. The temporary ultimates of science rapidly become penultimates.

MENTAL QUALITIES IN RELATION TO RESEARCH CAPACITY

Probably an enquiring mind is the special quality needed for research, by which I mean original research and not merely the hack work of the technician. Let me first try to analyse the mental processes on which this depends.

There seem to be two main attributes involved in human cerebration, the power to memorize facts and the power to correlate them. Whether the widely differing capacity of different individuals in these two directions depend on the number and quality of brain cells to store facts and on inter-connecting fibres to correlate facts and experience is not pertinent to this paper although it is a temptingly simple illustrative view. Certainly these two qualities can be widely divorced. We all know people with wonderful memories who are intensely stupid. We all know students who can write wonderful examination papers from memory but who are lost when they have to apply this to practical problems involving reasoning and correlation of thought. This is all too obvious in clinical medicine where the mere memorized store of text-book knowledge cannot be brought to bear on varying problems of human dis-

ease which seldom fit into an exact academic picture. The pure memorizer is lost. Then there are the "intelligent" and the "intellectual" types. When dictionaries are consulted, we find that the two words are similarly derived and defined, but to me there is an enormous difference of meaning, pertinent to our enquiry into the special quality of the research type of mind. After all we can say that a dog is intelligent, but never that it is intellectual.

To me intelligence connotes, apart from a good or poor memory, a quick, immediate and right mental response in thought and action to presenting problems and circumstances, based mostly on rapidly applying previous experience and knowledge to the problem in hand. The intellectual person, and he is usually intelligent too when occasion demands but not necessarily quick, has special qualities of deeper and more probing thought. He is always enquiring more profoundly into accepted conventions and explanations. He has wider co-ordinations, delves deeper into accepted explanations, sees new relationships in disconnected facts, has a constant 'why' in his adult mind, a questioning of accepted convention of thought and ideas which do not seem to fit into facts and their relations as he sees them. He is a constant questioner and often a rebel both in society and in science. This is the essence of the enquiring mind, the intellectual mind. It criticises, freshly relates and reco-ordinates relationships which are accepted by merely intelligent minds: it makes a relating generalisation between two previously unco-ordinated phenomena. Often such inspirations, shall I call them, come easily like spontaneous sparks and such I think must have been Banting's about his insulin research. But when this type of mind sets itself deliberately to such a new critical synthesis, this is the hardest scientific task a brain can impose on itself in my opinion.

THE REQUIREMENTS FOR GOOD RESEARCH

Granted the enquiring mind whose qualities I have tried to analyse, how does a worth-while new idea in research arise and what is needed to bring it to fruition? The immediate stimulus usually arises in one of two ways: either from a fresh critical analysis of accepted theory, often arising from a new discovery in a related field, or from a new observation, perhaps a chance one, suggesting that the accepted explanation of a phenomenon cannot stand. A worth-while new idea can hardly arise in a mind not fully versed in the subject. If it does—and some have arisen in the minds of critical young students, fresh minds on an old problem—the next step is a thorough search of all published work which may be pertinent and often found in several languages. This may take months and may result in the discovery that the idea has been thought of and tried out before. I remember in 1924, when trying to produce food tables for diabetics, spending months in finding out what figures existed for carbohydrate foods in various tables and discovering that they varied by as much as 300 per cent. This realization was the starting point which led to a re-analysis, first of carbohydrate by McCance and myself and then of all foodstuffs by McCance and Widdowson for several years.

After this comes inevitably to the enquiring mind a fresh explanatory hypothesis, an informed guess on a new possibility or probability, which is as often wrong as right, at least in my personal guesses at how natural processes should work. The ways of nature are seldom such as my logic would expect. Next comes the planning of observations or experiments, often complex and technically difficult, to prove or disprove the idea. In this the investigator must be fair and open minded and guard himself against a bias in favour of the darling child of his own imagination. It is all too easy to plan experiments to prove a point and all too natural to gloss over a few discordant results or to weigh the evidence too much in favour of one's hypothesis. This is the lawyer's point of view, I often feel, to prove a point whether it is right or wrong in favour of the client and an idea. The scientist, and especially the young with too vast an enthusiasm, should be aware of this danger. A false finding, which appears right by his own proving, may perpetuate error for years and has to be laboriously disproved. He should therefore be made aware and keep himself aware of the necessity of the strictly controlled experiment to curb the bias of his enthusiasm. And he should know enough about mathematics to apply, or have applied, the science of statistics, first in the planning and later in the criticism of the validity of his findings.

Then there are other more material things needed. A pair of good hands with delicate touch is as necessary as clear mental qualities for performing the many fine techniques needed; the delicacy of touch required for surgery on smaller animals is infinitely more exacting than in human surgery. Good technical facilities in a well equipped laboratory are equally essential nowadays, for the simpler apparatus of the past has become inadequate for most research projects. These now involve the use of all kinds of electrical and other mechanical apparatus of extreme complexity—or so they seem to me who can hardly name, and much less understand, them.

Another requisite, for the young at least, is critical guidance and supervision by a wise and kindly director. This is usually necessary from early criticism of the idea behind the research, right through the difficulties that commonly arise at all stages in an investigation, to the final preparing of the results in a logical and well written paper—perhaps the hardest part of all in which superior guidance and strict criticism is necessary. Brief, clear and good writing is a stumbling block to many. One practical point of value which I learned from bitter experience myself is the wisdom, when results are beginning to shape and long before the end of the investigation, of writing up the results and criticising the tentative conclusions. One usually finds that some unforeseen point has been omitted which can easily be included in the investigation at an early stage but is difficult to incorporate later when the experiments are nearly concluded with some uncertain point omitted. It is depressing and sometimes impossible to restart at the final stages. Another point in writing a highly specialized paper or giving a communication is to start with a brief and simple explanation of the background and aims of the investigation to those readers or listeners who are unversed in the subject. I have often sat bemused and ignorant of the meaning of a specialized communication when a few general explanatory sentences would have removed muddledness and boredom.

Furthermore the investigator should be able to work in a state of financial security. Rich he will never be unless through some of the paths of industry, but none should be overburdened by the financial strain in meeting reasonable family responsibilities. This remark in no way belittles the vast importance of enlightened industry in supporting fundamental research in so many fields. But institutes require large resources to fill their establishments with active and satisfied workers. Many a beautiful library has been built and no money left to buy books!

ERRORS AND WASTED ENERGY IN RESEARCH

In reading or dipping into the thousands of articles published each year on my own and other subjects in biology and medicine, I am depressingly struck by the triviality and pettiness of all too many. Perhaps a major cause of this is the importance of having some research publications to lead to promotion and success in academic posts, often mainly teaching ones. Even in appointments for clinical posts in Teaching Hospitals, the background of publications often outweighs more important teaching qualities: "I must do research and publish a thesis to make my B.Sc. into a D.Sc., and so get on in life."On the other hand, early activities and discipline in research projects are of great value whether the future leads mostly to teaching or more to research. I, at least, find it impossible to read all papers even on my own subject. How does one judge whether an article is worthy of serious study? Partly from the critical calibre of the journal in which it is published; partly from the centre from which the publication comes and the acknowledgement to a director who is known to be critically concerned; partly to the opening paragraph and largely to the summary. Many papers fall by the wayside in satisfying these criteria. I think it is essential that ideas for a piece of research should be rigorously criticized from its inception to its end. This should not be so harsh as to exclude any new idea with a possibility of eliciting a new truth from a different angle. I have often wondered what would have happened to Banting's original idea about insulin if Macleod had refused his support. However, I feel certain Banting would have got on with it, somewhere, somehow. But would he have found another Best needed for the duet of success?

Poor technique and poor facilities lead to much error and poor work and need not be mentioned again. I should like to repeat my previous warning against emotional bias in favour of one's own hypothesis which leads so many investigators to false conclusions.

Finally, from what we have seen of this noble new institute and from what we know of its ideals and directorship we are sure that this new centre has all the qualities, material and spiritual, to make Toronto even more inspiring in physiology in the next than in the last half century.

Memorable Experiences in Research

Distinguished scientists present at the scientific session held in connection with the formal opening of The Charles H. Best Institute were each asked in turn by Doctor Best "Which of your scientific investigations has given you the most satisfaction and pleasure?" Their replies follow.

E. D. Adrian, Ph.D., President of the Royal Society, London

It is a very great honour to take part in this presentation. I'm not really very clear what you would like me to do, but I thought it would be best merely to describe one day's experiment which was, to me, an exceedingly enjoyable experience. The pleasure came not so much from doing the work as from realizing suddenly that I had found a way of doing a great deal more. I'm afraid that the argument will be mainly concerned with the techniques of electro-physiology, but it does illustrate the way things go sometimes without the need for any excessive hard work or excessive thought.

It was in the early 20's. I had taken up electro-physiological research on the central nervous system and had spent a great deal of time making string galvanometer records of action currents in the hope of being able to find out exactly what was coming down the nerve fibres when the muscle contracted. We knew then that nerves sent down nerve impulses as signals, but we didn't know anything about the way in which the impulses would follow one another. We didn't know whether they came at a high frequency, or at a steady frequency. We didn't know whether the frequency varied or not. In fact, we didn't know at all how the nervous signals were controlled. Alexander Forbes had been working with me in Cambridge and I had learned a great deal from him about string galvanometers and about mammalian preparations, but the experiments I had started became more and more unprofitable. You know the sort of thing that happens—they became more and more complicated and the evidence more indirect, and after a time it was quite clear that I was getting nowhere at all. But it was fairly clear at that time that the valve amplifier was going to make it very much easier to record action potentials, particularly very small ones, and there had been various descriptions of valve amplifying arrangements. In particular, Gasser and Newcomer had used a three-stage one to record action potentials in the phrenic nerve. I had rigged up a single valve one, but it wasn't much good, so having decided that I was getting nowhere, I wrote to Gasser for the details of the arrangement he was using for the phrenic. He was then beginning his studies with the cathode-ray oscillograph on the action potentials of nerve fibres of different sizes, but he gave me a full description of the amplifier that he and Newcomer had used, and I built one to much the same pattern. I knew very little about it and was rather afraid of all the complications in it. When it was ready, I decided to test it using the capillary electrometer which was in the laboratory, built by Keith Lucas about fifteen years before. I used the capillary electrometer because, although it wasn't as sensitive as the string galvanometer, it had the great advantage of being more foolproof in that it wasn't so easy to break the string if you overloaded it. The amplifier had to be treated with great respect, as in those days the valves were terribly microphonic. The arrangement I had gave a magnification of about 2000, so I set up a pair of

non-polarizable electrodes in a shielded chamber, and put the normal accompaniment of physiological research, the frog's nerve-muscle preparation, on the electrodes, to see whether I could get a steady base line. Well, I was distressed, but not very greatly surprised, to find that the base line wasn't a bit steady. It was oscillating rapidly all the time. As soon as the circuit was open there was this constant rapid oscillation going on and I naturally suspected that I was picking up an artifact from somewhere and that I should have to pull the whole apparatus down and stick it all together again and go on for another month or so, getting no results.

I began re-adjusting the apparatus, and then I found that sometimes the oscillation was there (it was a fine, rapid affair) and sometimes the base line was quite steady. There was a ray of hope, and after trying various arrangements, I found that this little oscillation was only there when the muscle was hanging down quite freely, from the knee joint of the frog's nerve-muscle preparation. If the muscle was supported on a glass plate there was no oscillation at all and the base line was quite steady. The explanation suddenly dawned on me, and that was a time when I was very pleased indeed. A stretched muscle, a muscle hanging under its own weight, ought, if you come to think of it, to be sending sensory impulses up the nerves coming from the muscle spindles, signalling the stretch on the muscle. When you relax the stretched muscle, when you support it, those impulses ought to cease.

I don't think it took more than an hour or so to show that that was what the little oscillations were. I was able to make photographic records of them, and within about a week I was nearly certain that many of these oscillations were action potentials coming up sensory fibres in the nerve, and what was more, that many of them came from single nerve fibres and that by some extension of the technique it ought to be possible to find out exactly what was happening in single nerve fibres when the sense organs attached to them were stimulated.

That particular day's work, I think, had all the elements that one could wish for. The new apparatus seemed to be misbehaving very badly indeed, and I suddenly found that it was behaving so well that it was opening up an entire new range of data. I'd been bogged down in a series of very unprofitable experiments and here suddenly was the prospect of getting direct evidence instead of indirect, and direct evidence about all sorts of problems which I had set aside as outside the range of the techniques that one could use. The other point about it was that, as I said, it didn't involve any particular hard work, or any particular intelligence on my part. It was one of those things which sometimes just happens in a laboratory if you stick apparatus together and see what results you get.

Detlev W. Bronk, M.D., President, Rockefeller Institute for Medical Research

Because I was a construction engineer before I was a physiologist, it gives me a special and nostalgic pleasure to speak to the accompaniment of constructive sounds of building still going forward and in this auditorium hastened to completion for this occasion. This is symbolic of the creative energy of Charles Best.

I have found it difficult to choose from among the scientific adventures that have comprised a happy and a satisfying life for me. I have therefore chosen to speak of a sequence of experiences. I have done so with the hope that my remarks will have the simple value of revealing how research may be directed by the unplanned events of life. For I believe, as Sir Lionel Whitby said yesterday afternoon, that the course of research is directed in no small part by subtle unplanned influences and undirected curiosity. My experiences have persuaded me that the spirit of research is a fundamental motive in human life.

I had the good fortune to be educated as an electrical engineer with an exciting interlude as a naval aviator. But when I came to the practice of my profession, I found that I was more interested in the nature of matter and physical phenomena than in the application of such knowledge to the solution of industrial problems. This led me to graduate work in physics.

I doubt whether any young man of my generation was less interested in the nature of biological processes than I, or so poorly informed. My indifference to such elements of a normal curiosity was shaken by an accidental injury to one of my eyes which aroused me to admiring

wonder regarding the mechanisms of the human body. They excited my engineering instincts. Thus I began my adventures in physiology at the University of Michigan.

Because I had a father who had spent four happy years in graduate study on the continent of Europe, I had the feeling that preparation for an academic career was incomplete without such a supplement to an American foundation. But English literature had fostered the development of sentimental ties which pulled me more to England than to my father's European Alma Maters, and especially to Cambridge, as did pictures of its architectural beauty.

The appeal of Cambridge was greatly strengthened by the exciting experiments which have been described this morning by Professor Adrian. For not only was the spectacular significance of those studies of nerve messages readily apparent to even the beginner in physiology, but they also involved the use of electronic amplifiers, and it happened that a few years before I had had the privilege of giving one of the early graduate courses in electronics because the professor in charge had gone on sabbatical leave. So I was drawn to Adrian's work by the feeling that my excursion into physiology would be aided by special knowledge in another field. The threads of circumstance were beginning to be woven into a satisfying fabric of research.

When I arrived at Cambridge to begin the happy associations and friendships I have now enjoyed for a quarter century, the first phase of Adrian's work on sensory receptors was drawing to a close. It was then that he suggested we investigate the possibility of recording the discharge of impulses from single motor nerve cells. For this, the rhythmically excited fibers of the phrenic nerve seemed ideal, for we thus avoided the hazards of artifacts from electrical stimuli which plagued the amplifiers of those early days. One more thread led to a useful past, for my first research in physiology had been guided by Gesell to the excitation of the respiratory center.

Some years later, when I was at the University of Pennsylvania, I happened to receive from Pennsylvania State College an invitation to give the Joseph Priestley lectures of that institution. I decided to describe the work that Adrian and I had done and the things that I had gone on doing in the Johnson Foundation. But it occurred to me that I should be prepared to make some appropriate and related remarks about Joseph Priestley's interest in the possible physiological effects of oxygen at the beginning of my lecture series. This and my previous work on the discharge of impulses in the phrenic and intercostal nerves aroused some latent interest in the oxidative metabolism of nerves and its relation to their rhythmic action.

But it was by chance that some advertising literature describing equipment for polarographic determinations came to my laboratory table. As I casually studied this circular, it occurred to me that polarography might be a means for measuring the oxygen consumption in peripheral nerve and in the central nervous system. If that could be done, thought I, I should have appropriate and significant material for a series of lectures in memory of Joseph Priestley. That was the beginning of the investigations Brink and I and our colleagues have directed to the electrochemical determination of oxygen concentrations in the nervous system with a high degree of spatial and temporal localization and accuracy.

That was in the dark days of 1939 and 1940. I was becoming much distressed by American colleagues who seemed to me to be inadequately aware of the great danger we were facing and of our responsibility with you of the Empire for our common defense. I was, I suppose, in part moved to this concern because of the happy days I had had in the laboratories of Adrian at Cambridge and Hill at London. Be that as it may, I desperately wished to do something useful to withstand the Nazi's perilous assault. Because of our oxygen studies, I began to think about the special requirements of submariners and aviators for oxygen. We began to shift the use of our polarography methods for studying oxygen concentration in the nervous system and our study of motor and sensory nerve impulses to their military implications and applications.

Not long after that, I was reminded by the United States Air Force that I had been an aviator before I became a physiologist and it was now my responsibility to join in their operations. This I gladly did. I soon realized with satisfaction that the needs of those urgent days did not dissociate me completely from my recent scientific interests. For Adrian's experiments, which first aroused my admiration in nervous mechanisms, dealt with the effects of gravity and tension on the organism. In the case of aviators, impulses were initiated by the high forces developed by internal combustion engines and this gave rise for the necessity of anti-acceleration suits. The reason why it became necessary to develop equipment which would adequately supply oxygen to our aviators who flew their missions high over the Nazis' European fortress was because there was not enough oxygen present at those high altitudes to keep alive the nerve cells which Adrian and I had been studying. So,

too, were the nervous mechanisms of vision intimately concerned with night flying techniques and the nerve impulses from the vestibular apparatus were related to problems of instrument flying and the early instruction of fliers.

Throughout those four rewarding years which marked the end of one era of my research and the beginning of another, I had the gratification of seeing adventures in aviation, engineering, physics, nerve physiology and biochemistry converge in one undertaking.

The lessons I would draw are these. To follow one's curiosity is more satisfying than to follow the planned direction of another, for no one can chart the course of exploration through unexplored territories of knowledge. To specialize too early and too much denies one the adequate preparation for unanticipated adventures in science where there are no natural boundaries or departments of knowledge.

Charles Best has been thanked for many things. He has been lauded in terms he well deserves. I would add my gratitude for his encouragement and his willingness to listen, and to have his students listen, to the enthusiasms of one who had ceased to be an engineer and physicist and had not yet qualified as a physiologist.

Sir Henry Dale, Past President of the Royal Society, London

Like those who preceded me in this series, and I suppose like those who will follow, I felt a bit puzzled in considering how I should treat this attractive invitation, to say something about that one of my scientific investigations which has given me the most satisfaction and pleasure. You see, there are all kinds of satisfaction and pleasure which one can get out of scientific work. One of the very greatest satisfactions is that of working in happy comradeship with good colleagues. On those lines, I should be tempted to choose, particularly in this connection, the opportunity which I had to work with Charlie Best and Joseph Hoet back in 1925-1926. It certainly gave me much satisfaction and pleasure; but I'm not going to choose it for this occasion, because, for one thing, we've naturally heard a good deal during the past two days about insulin and work on insulin; and another reason is that I never considered that to be one of my scientific investigations.

My friends will remember that I was taking an interest in what they were doing, and occasionally lending a hand in a particular technical operation; but I had always thought of it as essentially their work, and nothing has touched me more, in all my experience, than to have them come to me, when it was done, and insist that I should let my name appear on what I had regarded as a paper of theirs. This I had never intended. It is an easy thing, you know, for a senior to make a generous gesture to his juniors, in that sort of position. I know from my own memory, however, that it is not at all so easy for the juniors to be generous to a senior, and to have their credit diluted by introducing the name of a senior man. Well, I resisted as long as I could, until finally they said, "We are not going to publish it unless you put your name on it with ours."

That's a very, very happy memory; but I think that, for the present purpose I ought to concentrate on a different experience, and one which has just been brought rather vividly to my mind and has given me a great deal of satisfaction in retrospect; because I've only just come from a very lively and interesting symposium in Philadelphia, in which contributors from a number of different countries presented and discussed, greatly to my interest, even my excitement, new evidence bearing upon what the organizers of the symposium called "neurohumoral transmission." That is not a word that I pronounce very easily. I've always called it, rather more briefly and simply, "chemical transmission,"—the transmission of the effects of nerve impulses across synapses of various kinds, and other neuro-effector junctions, by the liberation of stimulating chemical substances. I feel bound then to choose, for my topic, that observation of my own which appears to be having the most vigorous development in other hands at the present time, namely, my observations on acetyl-choline, which revealed its intense and evanescent parasympathomimetic actions on various forms of involuntary muscles and glands, and then on autonomic ganglia and voluntary muscles.

I didn't discover the action of acetyl-choline. That was discovered by another friend of mine, the late Reid Hunt, whom I first met when we were both young men together, working in Paul Ehrlich's laboratory in Frankfurt. For years I hadn't thought very much about an ob-

servation which he had made in 1905-1906, in which he found that acetylating choline immensely increased its depressor activity, but didn't go any further with the analysis of that activity. Hunt supposed that it was entirely due to a weakening of the heart's action. He had been studying extracts of the suprarenal gland, estimating the amount of choline which they contained, and had found that they had a much stronger depressor action than could be attributed to the amount of choline which he could extract. I have very little doubt that the extra activity with which he was concerned was really due to the presence of the widely distributed histamine, the existence and action of which were not known at the time. Hunt, however, rather curiously, thought that it might be due to some derivative of choline which he hadn't been able to isolate. And so he got his friend Taveau to make a number of choline derivatives. The easy ones to make were the esters, and among these they easily picked out the acetic ester, acetyl-choline, as the one having a very intense depressor activity. In later years Hunt examined whole ranges of choline esters, and never found another one as intense in its depressor activity as acetyl-choline. At that time I read rather widely in physiological, pharmacological and medical literature, and I had a fairly retentive memory; but this particular item, which I had obviously noted at the time, had sunk into a subconscious layer of my memory, and I'd practically forgotten about it.

Then, about 1913, I was interrupted in the course of some other work which interested me. I was working then in a laboratory supported by industry, the Wellcome Laboratories, and I was interrupted by the arrival of an extract of ergot from the factory, with the request that I would test it, to see if it was suitable for clinical use. I thought this a nuisance, but I knew by experience that, if I postponed action, it would only make it worse, that I should get a series of reminders and things would pile up. So I said to my technician, "Bring along a cat and I'll do this at once." The cat was anesthetized and arrangements made for recording its arterial blood pressure in the conventional way, and I injected the customary dose of one cubic centimeter of this extract in the vein. And the cat's heart stopped dead. I thought, "Oh, clumsy fellow, you've injected a bubble of air into the circulation, and it's got into the coronary arteries, and that's that." I was turning away, to hang up my laboratory coat in disgust, and thinking, "I shall have to do another one now," when, out of the corner of my eye, I saw that the cat's heart had begun to beat again; and, presently, the blood pressure was completely restored. I thought that I might as well try it again; so I gave another cubic centimeter, and exactly the same thing happened again. Then I began to take notice. I thought that I'd never seen an effect quite like this before, with an ergot extract, or any other. I had better see what this extract would do to other sorts of organs; and I tested it in the usual sort of routine, on isolated strips of rabbit's intestine, perfused frogs' hearts, and so on; and presently there began to be built up the picture of a general parasympathomimetic action. Then it occurred to me that ergot was a fungus, and after all, muscarine, the classical example of a substance having that sort of action, came from a fungus. So I called my young friend, Ewins, who was my chemical colleague at the time, and I said, "Ewins, I'm going to condemn that batch of ergot anyhow. Nobody could conscientiously allow it to go for human treatment; but we'll keep it for research. You go ahead and see if you can get anything like muscarine out of it." Presently Ewins got a pinch of platinum salt, a few milligrams, of the active thing. It had the action which I had noted, but it was a very much more evanescent action than that of muscarine; and I began to suspect that it couldn't be muscarine itself, and that idea was accentuated by some other experiments. I dissolved some of it, freed from the platinum salt, in Ringer's solution, and perfused a frog's heart with varying dilutions on a warm day; and in a few hours the activity began to diminish and finally disappeared. I went down to Ewins and said, "Look here, that's a very unstable thing; in a weakly alkaline solution it just vanishes."

Ewins said, "Sounds like an unstable ester of some sort, doesn't it."

I said, "It does."

He said, "We'll never identify it. We've only got those few milligrams, and we can't do anything with that amount; so we'll just have to leave it there."

And then, as I was getting into bed that night, suddenly, from some lower subconscious layer, there whirled up into my consciousness the memory of Reid Hunt and the acetic ester of choline. So I went down to the laboratory the next morning rather earlier than usual, from eagerness; and I caught Ewins and said, "Ewins, I wish you would get some choline and acetylate it for me. Let's have some acetyl-choline."

He said, "Oh, what's all this about?"

I said, "All right, my boy, you do it and we'll see."

And of course, there it was. And then, as I went on, there was a link-up with an earlier memory, and another friend, still my friend and colleague in other connections—T. R. Elliott. As long ago as 1904 when he was a postgraduate in Cambridge, before he had begun his

medical qualification, he published a remarkable paper on the action of adrenaline. It is quite a physiological classic, and, even before that, Elliott had daringly put forward what seemed at that time an almost preposterous suggestion, namely, that the only way to explain the remarkable correspondence of the actions of adrenaline with those of the sympathetic nerves, an action which survived their degeneration, was to suppose that, when a sympathetic impulse reaches the ending of a nerve fibre, it liberates a small charge of adrenaline. And here we had a substance which imitated the actions of parasympathetic nerves even more accurately than adrenaline did those of sympathetic nerves. Of course, there were differences, the reason for which has again come to light quite recently. We know now that it isn't adrenaline, but noradrenaline which is thus liberated. Well, there was the new start of what has become a considerable story. Even Dr. Bronk has made interesting contact, I think, with the story, as it affects the function of acetyl-choline in transmitting impulses at synapses in peripheral ganglia.

Then as most of you know, another friend, Jack Eccles, formerly of Sydney and Dunedin, and now at Canberra, who had been the most truculent critic and opponent of any possibility of chemical transmission at voluntary myoneural synapses or at those in ganglia, suddenly, and for reasons which would never have made me think of chemical transmission, has now extended the conception to transmission at synapses in the central nervous system; and I expect that he will prove to be right. But I know very little about that, that's a matter for experts like Dr. Adrian. In any case this accident nearly forty years ago, the result of a request to test an extract of ergot, which I thought a nuisance, is still having some consequences which I find interesting; and I think that, on the whole, I take more pleasure and satisfaction just now in the thought of that particular experiment, than of any other.

Bernardo Houssay, M.D., Nobel Prize Winner in Medicine, Buenos Aires

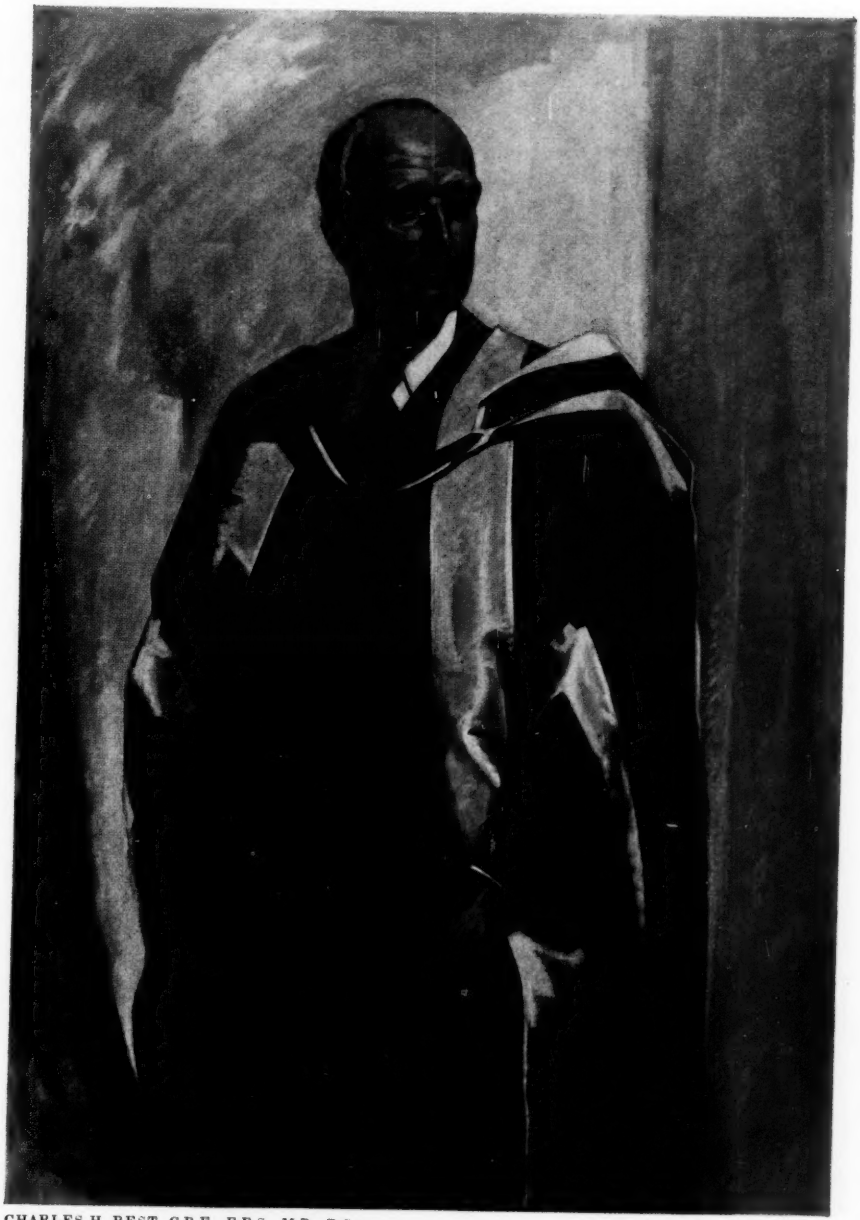
It is difficult for me to say which of the many investigations I have undertaken with hundreds of associates in the course of forty-six years of laboratory work in physiology, in four different institutes, has given me most pleasure and satisfaction. So many have been satisfactory and I have enjoyed them all so much that I am faced by an *embarras du choix*. The greatest satisfaction and the highest reward are to be found in the work itself, in the endeavor to overcome difficulties encountered in the course of research, in the achievement of some inkling of the truth.

When I was a medical student I used to make notes of problems I thought worth while to investigate. When a student of physiology in 1907 I became interested in the hypophysis; the next year, 1908, I started to do experimental work on this gland, and forty-five years later I am still experimenting in order to find out more about the functions and significance of this fascinating leader of the endocrine orchestra.

I have been interested in many very different problems. I can almost say that if opportunity arises to work in some special field my interest will be simultaneously awakened. When I worked in the Public Health Laboratories from 1916 to 1919 one of my duties was the preparation of antivenom sera. I thus became interested in the venoms of snakes, spiders and scorpions and studied their biological effects.

In 1921 Lewis came to work with me on the adrenals and in 1921 we had the satisfaction of proving that the adrenal cortex, not the medulla, was indispensable for life. At that time I worked with several associates on the factors regulating the secretion of adrenaline and more recently, of noradrenaline. At one time or another I have been interested in many aspects of the functions of each one of the endocrine glands.

Shortly after insulin was discovered, in 1922, Dr. Alfred Sordelli prepared insulin in Buenos Aires, and our group started to study its effects on the organism. Often the mail brought us published reports of results obtained by other workers on some of the problems we were investigating. It was, therefore, necessary to choose carefully fields which were not the object of study elsewhere. The action of insulin in relation to sympathetic and parasympathetic innervation and to the hormonal state of the organism was our field of choice. For this purpose the effects of insulin in animals deprived of the adrenals, or the thyroid or the hypophysis were observed. These glands had been the subject of research in my laboratory for several years, and at that time I had hypophysectomized dogs at my disposal. It was found that hypophysec-



CHARLES H. BEST, C.B.E., F.R.S., M.D., D.Sc.

By Cleeve Horne, R.C.A., O.S.A.

tomy considerably increased sensitiveness to insulin in dogs (with Magenta, 1924, 1927, 1929) and in toads (with Rietti and Mazzocco, 1924, 1925).

In the toad it is easy to remove the *pars distalis* of the hypophysis leaving the *pars nervosa* intact. This operation increased sensitiveness to insulin. Working with Miss Potick in 1929, I was able to demonstrate that implantation of the *pars distalis* (the equivalent of the anterior lobe of mammals) abolished hypersensitiveness to insulin in hypophysectomized toads, and increased the resistance to insulin in normal animals. This fact was confirmed in dogs by Miss di Benedetto in 1932.

In 1929 working with Biasotti, I found that hypophysectomy diminished the severity of diabetes caused by pancreatectomy in dogs. Implantation of the *pars distalis* (anterior lobe of mammals) again increased the severity of diabetes. The diabetogenic effect of the hypophysis was thus demonstrated. The severe symptoms of pancreatic diabetes were due to two factors: (a) presence of a hypophyseal hormone, and (b) a lack of secretion of insulin. The diabetogenic effect of hypophyseal extracts in mammals was demonstrated in 1932 simultaneously in three laboratories: in Evans', in Marine's and in mine. In 1932, I was able to provoke permanent diabetes by hypophyseal treatment in dogs previously submitted to partial pancreatectomy. Young obtained this effect in dogs with intact pancreas in 1937.

A paper reporting the result of this work on the role of the hypophysis in diabetes was sent to the United States, but was rejected by several journals, until in 1931 it was published in *Endocrinology*. The results were soon confirmed and extended, but even in 1935 many of my colleagues in the United States remained unconvinced of the existence of a diabetogenic activity in anterohypophyseal extracts because they used preparations which rapidly lost their activity at room temperature. I was able to give an ample report of this work as Dunham Lecturer at Harvard in 1936, and at the celebration of the tercentenary of Harvard University I delivered a lecture on diabetes as a disturbance of endocrine regulation. Today I cannot help feeling great satisfaction when I see the idea that diabetes is a disturbance in the regulation of the hormonal equilibrium which controls carbohydrate metabolism and is universally accepted.

These investigations gave a demonstration of the existence of metabolic functions in the anterohypophysis, specially important in carbohydrate metabolism and the pathogenesis of diabetes. Carbohydrate metabolism was shown to be regulated by a hormonal equilibrium, the disturbance of which may cause diabetes, hyperinsulinism, etc.

These results were achieved by the work not of a single person but of many working in close association. In many cases I cannot say what was my personal contribution and what should be credited to my associates. Apart, however, from the great satisfaction of contributing to increase knowledge in a field which is important for the understanding of bodily functions in health and disease, this work served to train a host of young scientists and to stimulate the development of original scientific research in Latin America.

I have had many other satisfactions. I have been honored by my colleagues who have chosen me to be their fellow member in scientific societies, some of which for centuries have been famous throughout the world. I have also been honored by high distinctions such as the Nobel Prize for Medicine which was awarded to me in 1947, and here in Toronto by the Charles Mickle Fellowship. The greatest satisfactions I have felt do not have their source in these high honors, however much as I prize them. In times of trouble and trial I have seen many men, young and not so young, of great scientific and moral worth, to the scientific education of whom I had contributed, give signal proof of loyalty to those ideals of truth and freedom for which I have lived. Scientists from all over the world, many from North America, also have shown and continue to show their solidarity in many ways, but mostly by helping me and my associates to continue our scientific work. This has been my highest reward and gives me my greatest satisfaction.

Elliott P. Joslin, M.D., Honorary President of the American Diabetes Association, Boston

I know why I am here today. You may not realize it, but I am here because Dr. Best's father was a practitioner of medicine, and so Dr. Best wanted to honour practitioners of medicine everywhere by asking another to come and talk to you this morning.

Unquestionably the piling up of case after case of dia-

betes has given me the greatest satisfaction, because by recording the facts of their completed life histories I proved to myself that aggressive, orthodox treatment of diabetes pays, and at the same time have shown my respect for what I have learned from Rollo, Bouchardat, Naunyn, Cantani, Petrén, von Noorden and a host of others. Do you realize that Rollo, who instigated treatment, published his book four years before my grandfather was born, in 1800? Not so long ago! You see how young the treatment of diabetes is! Each successive group of fatal cases has been a challenge to make the current group of living cases excel their predecessors. Such a challenge to oneself is harmless. No one is jealous of a doctor publishing his fatal cases.

I like to think how simply this all came about. Across the street from my boyhood home in Oxford, Massachusetts, lived the town historian, Mr. George F. Daniels. Without a college education he exemplified as high a type of scientific spirit as I have ever encountered. All his research was conducted unostentatiously, patiently and with scrupulous accuracy. He was started on his life's work by his father asking him, as he trudged back and forth to school, when he passed the site of the Indian Massacre of the Johnson family, to lay a stone on a pile to commemorate it. I can just remember that cairn of stones which he created and how as a little child I marched in the parade on a dusty summer's day in 1875 when the cairn was replaced with a monument. Subconsciously Mr. Daniels' cairn of stones and his faithful and meticulous history of Oxford influenced my whole life.

Today, I wish to show a report on a little less than a tenth of the cases coming under our observation, and to call attention to the fact that of 3,408 children, 2,806 are alive, as determined last week, and only 600 have died. I would call attention to the fact that of this group, there are only 23 that we have not traced in the last 56 years. Of the group 428 are living over 25 years, 131 are living over 30 years and 9 over 35 years. Of course I am so interested in statistics I would like to say more about the rest, especially the pregnancy cases, after what you have heard from Prof. Hoet this morning, but I will forebear.

It is given to few among the world's two and a half billion souls to make a discovery like our friend, Charles H. Best, who is honored here today. Perhaps in this century we could count the number on the fingers of our hands. Yet in contrast, each one of his students, even the humblest, the least gifted, if he should profit from that *master word* in medicine—WORK—uttered by that Canadian doctor, Osler, whom we all loved, could accomplish something of real value. That they should not be disheartened by the gap between teacher and pupil, I would add a phrase attributed to the German sculptor, Begas, "Jederman kann etwas thun was kein anderer Mensch kann." Each one can do something which no one else in the world can do. By the act of Charles H. Best at the age of 23 years, *ipso facto* the status of all medical students was raised from that of student to investigator.

Not alone length of days, but life more abundantly is what we all seek for diabetics. Since the establishment of the Quarter Century Victory Medal for perfection of body, eyes and arteries, there have been 49 recipients, of whom only 18 are our own. There are so many others who have almost achieved perfection that we are establishing a new class—a blue ribbon class—in order to recognize their high endeavor.

To protect the future of diabetics, we hope to erect in Boston a Hospital Teaching Clinic in which ambulatory diabetics can return at much less than routine hospital costs, receive instruction, encouragement and such development of character that life and health, hitherto unrecorded for diabetics, will be attained.

Wilder Penfield, M.D., Director of the Neurological Institute, McGill University, Montreal

It's a great honour and pleasure for me (a surgical interloper) to be able to be here to enjoy these two days and I would like, before answering your question, to pay tribute from my University to this University, and on a personal basis, to the career of my friend, Charles Best.

I suppose that the discovery of insulin and its elaboration has been a romance, the like of which there are very few in medicine. It will always be a romance, told and re-told from the time of the inspiration that came to Banting, up to the time of the building of the Banting Institute, and now of the Best Institute. We are seeing, in a way, the end of that romance and the

beginning of new work and new things and new discoveries which, we hope, will be equally important to mankind. Of course, when a clinician tries to add something to fundamental or basic research and knowledge, he is looked upon somewhat askance if he is a physician, but if he is a surgeon, he is looked upon askance by both the physician and the basic scientist. I think we should remind Dr. Best that he may have some need for clinicians in his new Institute and he should recognize, as Sir Henry Dale said yesterday, that his chief duty, as Director, is to oil the machinery of collaboration. I like that phrase, Sir Henry, I'm going to use it again. And I think that the Director of an Institute should be called an Oiler, and not a Director.

For a clinician, the greatest satisfaction in life, comes from his patients and his friendship with them. I am sure Sir Lionel will agree with me. On the other hand, satisfaction in scientific investigation is different. In scientific work, it seems to me, there are two forms of recompense. There is the thrill of pleasure that comes from a new observation that seems important, as Dr. Adrian described so beautifully in the wiggling of a line which shouldn't have wiggled. And there is the more permanent satisfaction that comes from eventual understanding. It is the thrill and excitement that an explorer must feel when he catches glimpses of a land that no one else knows, and there is the satisfaction that he must know when he occupies that land. The occupation can only be accomplished with a body of confreres and helpers.

In my professional career I've stood long hours at the operating table making careful records and using, as far as possible, methods of physiological precision. In hundreds of cases I have stimulated the exposed brain with a gentle electrical current while the patient lay conscious on the operating table. In each case, an effort was being made to find the abnormal area which was responsible for the patient's epileptic seizures and so to remove it and perhaps cure the seizures. I find it necessary to introduce such a preamble in order to illustrate the fact that in clinical medicine, one is never experimenting primarily, but only secondarily.

Once in a while during such an operation I have had the thrill and excitement of a new observation. I remember well the first production of vocalization. I was exploring the cortex with an electrode in that part of the precentral gyrus that lies between the area for movement of the contralateral thumb and the face, and when I set the electrode down on the gyrus the patient gave voice to a long-drawn cry like the cry of a newborn baby. It stopped instantly after the electrode was lifted. We were all startled, all in the operating room, including the patient. Each time the electrode was re-applied at that point, the result was the same. I realized then that man was different from other mammals in that he alone has a representation of vocalization in the cortex. Here was a mechanism which must contribute to his ability to speak.

I remember, too, when stimulation of the cortex deep within the relatively inaccessible fissure between the hemispheres produced movement and also vocalization, I guessed that there was another cortical area, a supplementary motor area. Then there was the day when an electrode caused a man to feel sensation in his arm, not in the well-known sensory area, but about six centimeters distant, just above the fissure of Sylvius, and the next stimulation, only about 2 centimeters lower, produced sensation in the leg. The man observed to me, "Those sensations were very peculiar ones." He found he wanted to move the limb in a certain direction but he was powerless to do so. I knew then that this must be the first demonstration in man of the second sensory area which Adrian had already described in animals.

Most unbelievable and most sobering of all were the psychical responses which came from time to time with stimulation of the superior and lateral surface of the temporal lobe. These were neither motor nor sensory but had to do with the mind. They appeared only rarely, with long months, sometimes years, between them. There was one woman who exclaimed that she heard an orchestra playing an air when the electrode was applied. The music stopped when the electrode was withdrawn and began again, twenty times over, when the electrode was re-applied to the same spot on the cortex. When I asked her to hum the air that she said she heard when I applied the electrode, she did so, verse and chorus. That music was passing through her conscious mind at the normal rate, and it was not a song which she knew completely at that time. It progressed much in the tempo of the orchestra, exactly as she had heard it playing years before. I realized that I was holding in my astonished hand the wand that would summon this particular recollection of past experience.

There have been other recollections, auditory, visual, or both, exactly as the patient experienced them and containing all the things to which he was paying attention at the time of the original occasion. Many of them had forgotten these experiences. There was a man who seemed to be laughing with his cousins, while his cousins were actually thousands of miles away in South Africa. There was a boy who saw men singing on a porch

while he was walking along a country road; a mother who heard her son playing in the yard and was aware of the sound of passing automobiles. There was the man who saw the lighted sign of a dairy, and after that the neon sign of a bottling works. These events were summoned with a vividness as though they were occurring in the present time while the patient was still conscious of being in the operating room. They were having what Jackson described as "mental diplopia".

Such incidents draw a thrill of surprise and pleasure, but I've felt such thrills before, with equal pleasure, while demonstrating the parasympathetic nerve supply to the brain of a monkey, while impregnating with silver the perivascular nerves on small cerebral arteries, or drawing with the aid of the microscope the alterations in neuroglial cells and realizing that here were appearances that reflected the state of health of the brain as though in a cytological mirror. I have felt such fleeting satisfaction during the anxious labour of some complicated surgical procedure.

Years ago, I knew it also in the youthful background of the football field, during the rough and tumble of scrimmage with the roar of exciting sounds. Life seemed to hold nothing finer, there seemed to be no more worthwhile struggle, than the crossing of Yale's goal line. But one lasting truth I learned at that time, and that was that success comes with teamwork and satisfaction with common effort.

Professor Best has asked the question, "Which of your scientic investigations has given you the most satisfaction and pleasure?" and I have turned back to reconsider the different thrills that have come at different times, but those were not the most lasting satisfactions. I think the most lasting satisfaction is that which comes during a review of clinical observations, at a time when you can stop considering the needs of each separate patient, and when you can see things fitting together into a whole. It is the fitting into a general picture of these disjointed and occasional observations of a physiologicai type, particularly the psychical observations on memory, that have given me the greatest satisfaction.

It becomes apparent and it must be so, that there is in the two temporal cortices a recording mechanism, like a wire recording if you like, which is recording all those things to which we attend during our conscious life, from the time of the dawn of consciousness to the grave, and that the recording mechanism must pass through a central integrating system which integrates for the whole nervous system and projects it in some way to each temporal lobe, projects it so as to leave behind the pattern which can be activated by an electrode, to show in complete detail, all of those things to which a man attended at that time.

Nothing is lost, if one may judge from the occasional elements that can be activated electrically, nothing is lost in the mechanism of the nervous system. A great deal may seem to be lost to our voluntary attempt to re-construct. For a few seconds or a few minutes any of you can recall your experience as the electrode would recall it. You can close your eyes and see this room, but you will not be able to do so later. But the record is still there, and your memory recalls a generalization of and a reclassification of similar memories.

I think, Dr. Best, the greatest satisfaction I have had is in seeing these incidental observations on the cortex fall together in a reasonable way.

Sir Lionel Whitby, Vice-Chancellor of the University of Cambridge

It is often the function of the last batsman to have to gather very valuable runs, but those who have batted before me have done so so effectively that there is almost nothing for me to say in trying to answer this very difficult question posed by Charles Best. However, I am glad to say that I have had a most happy and active life, an extremely varied one which has thrown me into wars as a combatant and non-combatant, into the palaces of kings and into all sorts of situations, and I have had therefore some difficulty in picking out from that varied experience that which I think has given me the most satisfaction. Sir Henry Dale has said that there are so many aspects of satisfaction, that of happiness with colleagues, that of friends which one has made, and so on, and it is quite certain that one period of my life to which reference was made yesterday, (that of the last war) made for me so many friends that I often regard that time as having given me the most satisfaction and happiness.

However, there was a certain period of nearly five years in my life in which my main interests were in therapeutic experiments and I will choose an incident from this period because it is slightly romantic, it shows that one has occasionally to exercise imagination, and it shows that it isn't always hard work which leads to a result, that in fact there is something to be said for the social side of life, including good living and enjoyment.

It was a relatively short five-year period of my life and out of this I was spun, as was said yesterday, to an assignment for war purposes, and to which I have therefore never had an opportunity to return. But soon after Domagk's discovery of prontosil I became interested in trying to extend it for the purpose of treating pneumonia. As Sir Henry has hinted, I was at that time associated with a delightful and very able chemist, Dr. Ewins, of Messrs. Ray and Baker (he had moved from Wellcome) and it was his part of the work to synthesize new compounds, as it was mine to test these biologically. We had a good deal of discussion over the years as to which compounds would be most likely to yield a successful result, but it wasn't easy to get a lead. But we eventually came to the conclusion that alterations at one end of the sulfonamide molecule were likely to be more productive than alterations at the other end. That particular observation eventually proved to be true and was exploited. But it was heartbreaking work. One never seemed to get anything much more active than sulfonamide itself against the infection known as the "Captain of the Men of Death".

However, in the summer of 1936 there was in England an International Serological Conference which I had attended, and which had its annual banquet to which we were all summoned as the final social event. After this banquet I emerged from the Trocadero Restaurant soon after midnight and instead of taking a taxi home I took it to the laboratory. Now I ought to say that experiments of the type which we were then doing were made on batches of mice, and it was an advantage to have an assistant to hold the mice, otherwise there might be damage to the operator from a bite. The experiment consisted of feeding the mice by stomach tube, a delicate operation, since the stomach tube was made of metal and there was a danger of perforating the esophagus of the animal. I proceeded to the laboratory, looked at the mice, and then fed them with my own hand. The score was about even. That is, I got two bites, and I perforated two esophaguses. Nevertheless, from that batch of two dozen mice, on the next day for the first time there was a significant increase in the survival rate, as compared with all the substances which had hitherto been tested. There was, of course, a bit of luck, because in the batch was sulfapyridine. It was a very heartening result, but of course, it needed to be repeated. It was repeated, but with no effect whatsoever, and so one simply thought at first that the good result had been mere chance. There wasn't very much of the compound available, but after some two or three days it suddenly occurred to me that there was a distinct difference between the first batch of mice and all the other ones which had been tested. And that difference was, in fact, the same in the case of everybody who was working on the problem throughout the world, since everyone used roughly the same procedure. Our technique was to arrive at the laboratory at 8 in the morning, start the experiment, feed the mice and then give another feeding six hours later, and another before we went home about 6 in the evening. After that, the mice were left to see the night through. It occurred to me, of course, that the particular batch of mice, on account of the social event, had had an extra dose in the middle of the night, and that in fact proved to be the answer. To get an effect it was necessary to keep up the blood concentration by dosage in the night as well as in the day. That observation was, of course, eventually translated to the wards and those who have endured the discomforts of sulfapyridine treatment on account of an attack of pneumonia, will remember that they were awakened in the middle of the night in order to receive an administered dose.

Well, that fundamental therapeutic observation emanated from the chance of a dinner of the International Society of Serology in London. Perhaps I might say that, in retrospect, I have chosen this incident as giving me the greatest satisfaction, and I say this with all humility and diffidence, because out of that particular experience came calls to me to assist in the treatment of the pneumococcal infections of a patient, who was probably the most important person in the British Empire, during the past war.

Dedication of The Charles H. Best Institute

SPECIAL CONVOCATION

Preceding the opening of The Best Institute, a group of prominent scientists, present for the occasion, were honored by citations in a special convocation held at the University of Toronto. Citations were presented by Dean J. A. MacFarlane, Faculty of Medicine, as follows:

CITATIONS

To Detlev Wulf Bronk:

When the history of this era is written, I am sure that due tribute will be paid to certain great minds disciplined in the schools of natural philosophy, who have achieved important executive positions in the field of education and served their nation brilliantly in state and diplomatic capacities. Doctor Bronk has a long and distinguished record of teaching and research in the field of physiology and biophysics. He has woven his achievements into that amazing fabric which is the United States of America, and in so doing, has truly enriched and adorned its diverse patterns. His name is a familiar one in the universities of this continent, as it is also in many advisory committees of his own government. New work, new problems, new assignments have always attracted him. The directorship of the Rockefeller Institute of Research in New York City is his latest challenge.

Mr. President, I request you in the name of the Senate of this University to confer on Detlev Wulf Bronk, the degree of Doctor of Science, honoris causa, in recognition of his outstanding contributions to science, and as a salute through its retiring President to a sister institution in the United States, the Johns Hopkins University.

To Bernardo Alberto Houssay:

The value and significance of the research work of Professor Houssay of the Argentine was apparent early in his brilliant career. The high quality and importance of his researches have been recognized by his colleagues in other universities throughout the world. In association with one of his co-workers he was awarded the Nobel Prize in 1947. He is no stranger to this university; in 1945 he was awarded the Charles Mickle Fellowship, and in 1948 he delivered the Banting Memorial Lecture. In his own country he has held high the torch of academic freedom at a time in the history of nations

when the maintenance of such ideals has often meant sacrifice and sometimes suffering.

Mr. President, in the name of the Senate I request you to confer on Bernardo Alberto Houssay the degree of Doctor of Science, honoris causa, in recognition of his magnificent contributions to physiological research, and his great courage and steadfastness in the face of adversity.

To Elliott Proctor Joslin:

In each generation it is given to few men in the profession of medicine to demonstrate in their daily lives the ideals of their calling to their fellow doctors and to the world. Such a person is Dr. Joslin of Boston. To his colleagues, to his friends and to thousands of ailing humans he is indeed the beloved physician. Interested early in his life in the seemingly hopeless problems of diabetes, he welcomed with enthusiasm the advent of insulin and has established a world-wide reputation for his knowledge and wisdom in the management of disturbances of carbohydrate metabolism.

Mr. President, in the name of the Senate I request you to confer on Elliott Proctor Joslin the degree of Doctor of Science, honoris causa, in recognition of his great qualities as a clinician and teacher, and his untiring interest in the welfare of diabetics in his own country and throughout the world.

To Wilder Graves Penfield:

There is in this country occasional comment on the fact that we have, at least in numbers, borne some losses in the interchange of peoples between Canada and the United States. We are heartened, however, when we think on the stature of some of those American citizens who have come to dwell within our borders. Dr. Penfield, born in the western States, educated in New England, shared in the bounty of that amazing Britisher, Cecil Rhodes, and went to Oxford as a Rhodes Scholar during the First Great War. He interrupted his studies like so many others of his generation to serve with the allied forces in France. Since 1928 he has lived and worked in Canada, and since 1935 he has been a Canadian citizen and has received high honours at the hand of Her Majesty. He has established a national and world-wide reputation in the field of neurology and neurosurgery, and as one of our new Canadians, has adopted this country and the Commonwealth enthusiastically as his own. With his untiring energy and by brilliant scientific contributions, he has richly adorned the title of Canadian citizen.

Mr. President, I request you in the name of the Senate to confer the degree of Doctor of Science, honoris causa, on Wilder Graves Penfield, a brilliant scholar and writer, an experienced and distinguished surgeon, and a worthy representative of that great sister institution in Montreal, McGill University.

To Sir Lionel Ernest Howard Whitby:

In the dark early days of the recent war, men and women in Britain were often given new and difficult assignments. Lionel Whitby, with long experience and interest in haematology at the Middlesex Hospital School in London, was commissioned by the War Office to organize in southwest England a service for the collection and distribution of blood and other necessary intravenous solutions for the treatment of shock and wounds. Very shortly this magnificent organization directed by Brigadier Whitby was supplying not only the casualty centres in the south of England, but all those battlefields throughout the world where fought the sailors, soldiers and airmen of Britain and the Commonwealth. The British Army Blood Transfusion Service, under his direction, was a most important factor in the achievement of victory for the forces of the Allies. At the end of the war he returned to academic life in Britain, as he had done once before after suffering grievous wounds in the first Great War. Appointed Regius Professor of Physic in the University of Cambridge in 1945, he was asked to become master of Downing, his old college, in 1947, and in 1951 he was appointed Vice-Chancellor of the University of Cambridge.

Mr. President, I request you in the name of the Senate to confer the degree of Doctor of Science, honoris causa, on Sir Lionel Ernest Howard Whitby, a brilliant teacher and investigator, a leader in the field of education, a gallant soldier and a great citizen of the Commonwealth.

ADDRESS BY

SIR HENRY HALLETT DALE, O.M., G.B.E., M.D., F.R.S.

You have done me a great honour and one which I deeply value, for intimately personal as well as for more general reasons, in inviting me to take a leading part in a ceremony so significant for the University of Toronto and for its Department of Physiology. The achievements of that Department have already made a great contribution to the fame and the status of the University's Medical School as a whole, which has attained an outstanding position among the great medical schools of the North American Continent and, indeed, of the world.

The interest taken in the present occasion by the medical scientists of all the world, is manifested by the presence here today of eminent representatives of physiology, and of the associated branches of medical science, from many different countries; and included among your visitors are those leaders in different fields of medical research and teaching, and of their applications in practice, whom we have just greeted, Mr. President, as they received the University's Honorary Doctorate at your hands. All these by their presence today, bear witness to the significance which is attached, by the medical and scientific world at large, to the symbolic act in which we are about to take part.

We are here to dedicate, to the service of science, and of mankind, a new Institute of Physiology and Medical Research for this Medical School and University—an Institute which will be replete with the equipment, and with the potentialities for development, which these modern departments demand. In so doing we shall write the heading to a new chapter in the already impressive history of this University Department of Physiology, and of the Banting and Best Department of Medical Research. The latter Department was established by the Board of Governors of the University from a special grant made by the Legislature of the Province of Ontario in 1923, to honour the discoverers of insulin, and to provide opportunities in medical research for other young men.

For those who work in these departments and for their successors, we may feel confident that the opening of this new home for their activities, will inaugurate a new era of opportunities. The whole University Department of Physiology is to be moved to this new Institute. Of the Banting and Best Department of Medical Research, a part will remain in the Banting Institute, and a part will now find its home in the new Institute which we are here to dedicate. We all hope, Mr. President, that your own suggestion, of an appropriate structure joining the top floors of these two neighbour Institutes, and preserving the insulin memorabilia for the interest and encouragement of future generations, may soon be made effective.

Through its special association with his name, the Institute which we are about to dedicate will become, most fittingly, a lasting memorial to the personal achievements, the stimulating influence and the inspiring leadership of the present distinguished Head of these two Departments, Professor Charles Herbert Best. For since the early days when, as a young graduate in science, he shared in one of the greatest and the most widely influential, of all the great medical discoveries which this era has witnessed in such profusion, Professor Best's own researches, and his vitalizing influence on the work of his many able colleagues in these Departments, and even beyond them, have continued to make a major contribution to their growing reputation, and now, for more than a quarter of a century, have made Professor Best himself a central figure in this most recent and imposing phase of the development of Toronto's University Medical School as a whole.

As appears to have happened in others among the world's university centres, and especially in a number of those in England, the origin of what was to grow into the Medical School of the University of Toronto seems to be rather obscure, to have been somewhat irregular perhaps, according to our present notions, and, in any case, to have been the offspring of individual

enterprise. There is record, as long ago as 1824, of an advertisement by a certain John Rolph, announcing his readiness, for an appropriate fee, to give lectures and demonstrations here on anatomy and physiology; though no evidence seems to have survived concerning the facilities which he proposed to use for the demonstrations, or the numbers of those who thus early availed themselves here of this opportunity of instruction.

The enterprise survived in some form, however, so that it was able to resume its activity in 1843, to evolve then into what called itself the Toronto School of Medicine and, in 1870, to become the Medical Department of the Victoria University. Meanwhile, however, the College of Physicians and Surgeons of Upper Canada had been organized in 1839, and seems to have joined forces with King's College, with Dr. W. C. Gwynne as the Professor of Anatomy and Physiology in that combination. I gather that the history of this intermediate period is not known in detail, or with certainty; but there is a clear suggestion of a competition, of a kind familiar to anybody who has had contact with comparable developments in other English-speaking communities, between the professional organizations, on the one hand, and academic authority on the other, for a dominating interest in the control of medical education; until, in 1887, the absorption of three separate organizations into the Faculty of Medicine of the University of Toronto, happily laid at last a firm foundation for the development here of your present great Medical School.

A name deserving special mention, in connection with this succeeding stage of development, is that of Robert Ramsay Wright, who had come to the University from England, and had been occupying its Chair of Natural History, or Biology, since 1874. When the single Medical Faculty came into being in 1887, Professor Wright seems to have absorbed the teaching of Physiology into the duties of his Department of Biology. It may be that this association had a special significance, betokening something like a victory, perhaps, for the claim to allow Physiology to deal with the functional aspects of Biology as a whole; in contrast to the rival, professional tendency of those days, to restrict Physiology, in close association with Human Anatomy, to the narrower role of ministering to the direct requirements, in teaching and practice, of Medicine and Surgery. There is, in fact, no surviving record of what Professor Wright included in his course, but he appears to have had what passed in those days for a well equipped laboratory.

Perhaps I may be pardoned, however, if I venture, in passing, to doubt whether its equipment would be recognized now, by the research worker, the teacher, or even the student of physiology, as contributing significantly to its present technique—in these days when whole rooms full of complicated electrical circuits and electronic machinery, serving the needs of kathode-ray recording, ultramicroscopy, detective work with radioactive tracer elements, and so forth, appear already to have become almost the commonplace, standard requirements of experimental physiology; to the frequent bewilderment, be it confessed, of the less sophisticated physiologists of my own generation, brought up to regard an induction-coil of Dubois-Reymond's pattern, and Ludwig's kymograph, as fulfilling most of a physiologist's needs for special apparatus, until years still relatively recent. I think that we must suppose that the technical equipment at Professor Wright's disposal, when he began his course of Physiology, was of an even more primitive type; but, if we require evidence of his success in presenting such Physiology as was then known, in relation to a wide range of general biology, we can surely find it in the special interests and aptitudes displayed, in due course, by his most distinguished pupil, who succeeded him in the Chair of Physiology when it was eventually split off from Biology as an independent discipline, Archibald Byron Macallum—that typical Scottish Highlander, born of Gaelic-speaking parents in Western Ontario, who thus became the real founder of the separate Department of Physiology here. For the Physiological discovery with which Macallum's name will probably be longest associated, was that which brought to notice the highly suggestive, detailed similarity, between the relative proportions in which the different inorganic salts are present in the blood plasma of the higher, air-breathing animal types, including our own, and those in which these same salts may be supposed to have been present in the sea-water of earlier geological epochs, which provided the fluid circulating in the bodies of our remote marine ancestors.

I must not allow myself to dwell too long, however, on Macallum's great services to this School in those early days. Professor J. B. Leathes, who was later one of his professorial colleagues here for some years, in a very sympathetic obituary notice of Macallum and his career, gives a dramatic account of the victory achieved, at a crucial stage of the School's history, by a determined band of Scottish professors, led by Macallum as their fighting chief, which secured the recognition here of a sound knowledge of the preclinical and experimental sciences, as the firm foundation of the medical

curriculum. Macallum's enterprising mind was further ready to give early recognition to the potentialities of Biochemistry, of which he planned and conducted a separate course, in the Department of Physiology, as early as 1904. In 1907, at his own request, he became the first incumbent of a new Chair of Biochemistry, leaving the Chair of Physiology to Thomas Gregor Brodie, who came out from England to occupy it. Brodie was already well known as an important figure in physiology, and especially as a master, over a wide range, of its experimental methods.

During his tenure of the Chair, the Department received a notable improvement and extension of its equipment for various types of physiological research—for aseptic operations, for the care of animals under experiment, for the then comparatively novel electrocardiography, for the analysis of gases in the breath, and so forth. When war broke out in 1914, Brodie hurried back to England, believing, presumably, that he would there find a readier and more direct opportunity of serving the cause of Britain and her allies; but any plans in that direction were interrupted by his early and sudden death. After an interregnum, with several short-term appointments, the vacant Chair of Physiology was filled by the appointment of John James Rickard Macleod, who, after a training at Aberdeen and an appointment in London (England) had been holding the Chair of Physiology at Cleveland, Ohio. Macleod's tenure was, of course, to be one of historic importance, for the world reputation of the Department and of the Medical School to which it belonged and, less directly, for the advancement everywhere of physiology and experimental medicine. He succeeded to a Department unusually well equipped, by the standards of those days, for research in the general field of Physiology, including that of his own special interest in the problems of carbohydrate metabolism.

In this special field, Macleod had himself already made some sound experimental contributions to the then generally accepted canon of knowledge; and there could have been few, if any, who had a better command than his, of the voluminous literature of the researches and theories which dealt with it. When young Frederick Banting, therefore, with a recent surgical experience from war service, and little more than a student's knowledge of physiology, came asking, with a burning eagerness and the sense of a mission, for opportunity to make a new attempt to obtain, from the islets of the pancreas, the hormone, insulin, with the production of which speculation had long credited them, Macleod was well qualified to give him a discouraging account of the failure of many earlier attempts, most of them by workers of a much riper experience. It was a fair and proper warning; and it should be counted to Macleod's lasting credit that, having given it, he agreed, nevertheless, to give Banting also the desired opportunity. Possibly he had seen that methods then newly available, for measuring the minute amounts of glucose present in small samples of blood, might have produced a significant improvement in the chances of success for a further attack on such a problem. And it should be further remembered, in any case, that Macleod had produced a class of students well trained in these new methods of microanalysis, and in determinations of the respiratory balance of oxygen consumed and carbonic acid exhaled.

It was Macleod, also, who saw that, if Banting's attempt was to give any intelligible result he must have the cooperation of somebody with this recent biochemical training; and this recommendation was responsible for bringing Charles Best, recently graduated in Science, trained in the necessary biochemical methods, and himself rendered eager, by a family contact with diabetes, to do something for those whom it afflicted, into the historic collaboration. Frederick Banting supplied, on his part, the determined, unquenchable initiative, and an equipment with the necessary surgical technique. The collaboration was to be one of intimate understanding, with no question between the two participants of any but an equal sharing of its success. Matters having been thus arranged, Professor Macleod, still quite naturally sceptical of any successful outcome to the enterprise, left Toronto to spend the summer in Europe; so that it was in an otherwise deserted Department that the two young and inexperienced but determined enthusiasts, working at tremendous pressure through the hot summer months of 1921, taking turns to sleep on occasion, solved the main problem without further aid from, or communication with, anybody. As a result they had the clear evidence of the existence of insulin, and of the possibility of obtaining it in a separate solution, and of eliciting its effects by artificial injection, by the time Macleod returned from Europe.

A discovery of that major importance was bound to inaugurate something like a new era, in the history of the Department in which it was made. It led also to a much wider change, affecting the tone of general opinion concerning the possibilities of further advances in endocrinology and in its practical applications. The lack of any subsequent success comparable to Murray's effective treatment of myxoedema by the administration of thyroid gland, at Victor Horsley's suggestion, thirty years earlier, had produced an atmosphere of doubt and

pessimism about the likelihood of any further progress on these lines. There was a widely prevalent suspicion that the internal secretions attributed to other ductless glands might have no real existence, or that their active constituents might be secreted as fast as they were formed, or be very unstable, so that no other gland of this kind would, at any moment, yield sufficient of its specific principle to extraction, in a form making it accessible for investigation, or for administration to replace a deficiency. The discovery of insulin, the demonstration that, in spite of all theoretical doubts and difficulties, it could really be extracted, studied and effectively administered, changed the whole atmosphere of opinion to one of optimism and fresh enterprise. Progress in the field of endocrinology was resumed with an acceleration which has already produced a revolutionary change in our knowledge of hormones and their uses in therapeutics, and which still continues.

It would lead us far beyond the purpose of this occasion, however, to attempt to mention even the leading features of the practical development of the production of insulin, here in Toronto first, and then in other centres of different countries, or of the resounding success of its application in therapeutic practice. I wish that I had time, indeed, for more than a passing tribute to the importance of the part played at an early stage, in the discovery and elaboration of a method for separating insulin from the complex extract in a form suitable for clinical use, by J. B. Collip, now a world famous contributor to a much wider field of endocrinology and Dean of the Faculty of Medical Sciences in the University of Western Ontario. The discovery, by others, of the reactions of normal animals to insulin, was another factor of cardinal importance in facilitating this practical development. I ask your indulgence, however, to allow myself the personal pleasure of recalling that it was in connection with these practical developments that I paid my own first visit to Toronto, in September 1922, just 31 years ago, in response to a generous invitation, and as an emissary of Britain's Medical Research Council; and that this visit gave me the opportunity, while renewing some earlier friendships, to make new ones too numerous for individual mention. Macleod I knew already from earlier contacts in England; Banting I met for the first time, and admired for the force of his character and the fire of his enthusiasm; and I must allow myself to make one other exception, because of its special relevance to my intimate, personal pleasure in today's ceremony. The friendship which I then began with Charles Best has grown and strengthened through over 30 years now of an unclouded scientific comradeship—years which have included adventures in research which we directly shared, during more than one period of actual collaboration. And that friendship with Charles Best has been and still remains for me as great a source of pride and happiness, as any in a now long experience of friendships with many scientific fellow workers of great distinction.

When Frederick Banting and Charles Best had reached the immediate purpose of their historic collaboration, their paths in further research diverged. Banting, when the first chosen mark had been hit with speed and precision, by an arrow from a bow drawn almost at a venture, was not unnaturally disposed to aim directly at other targets, and to make similar attacks on other and unrelated medical problems, with the help of his devoted colleagues in the Banting and Best Department of Medical Research. The tragedy of his untimely death leaves us with no basis for an estimate of the likelihood of his further success by such methods. Best's instinct on the other hand, seems to have led him to take a continuing interest in the developments needed for the exploitation of their joint discovery in practical therapeutics. He thus came to take his full share, and eventually to give leadership, in work on problems arising in connection with the production and control of insulin, in the Connaught Laboratories as well as in the Department of Physiology. At the same time, he showed signs of the true genius of a systematic explorer, for obtaining full scientific value from observations which many might have passed over as incidental and irrelevant. I take pleasure in the thought that, when a visit to my laboratories had involved him in a study of the natural occurrence and distribution of histamine in the various animal organs, he was soon launched, with his colleagues here, on an investigation of the nature and distribution of an oxidative enzyme, responsible for the natural destruction of histamine, when liberated in the body. What appears to be a more important harvest of knowledge is still being gathered in studies, under his leadership, which had their origin in observations, incidental to the early work on insulin, of the infiltration with fat, and the ultimate degeneration, of cells in the livers of dogs from which the pancreas had been removed. This has led to an investigation of wide-reaching pathological interest, concerning the conditions conducive to such deposition of fat in the cells of vital organs, of its degenerative consequences, and especially concerning the so-called lipotropic substances—choline and methionine in par-

ticular—the presence of which is necessary in the diet to prevent this morbid deposition of fat.

When Professor Macleod retired from the Chair of Physiology here, largely on account of failing health, and returned to his native Scotland, I confess to have waited with some anxiety to see whether those responsible here for the filling of the vacancy, would recommend what seemed to me the obvious appointment. I hoped that too much weight would not be allowed to merely conventional ideas about years of discretion, or maturity of experience; and, in the event, I rejoiced to find that my hope was justified. At an unusually early age, Charles Best thus became the Professor of Physiology in this Medical School; and, so far from being weighed down by the load of responsibility which he had thus early in life accepted, he soon began to alarm some of his friends, who heard, only from a distance, that he had been induced to continue parallel, or in some cases, perhaps, overlapping responsibilities, for Physiology in the School of Hygiene and later in the Banting and Best Department of Medical Research, and, continuously, for advice and supervision in connection with more than one

Recipients of honorary degrees and participants proceed from the Special Convocation to the dedication ceremony of the Institute. From left to right (after the mace bearer): President Smith, Colonel Phillips, the Hon. Paul Martin, Sir Henry Dale, Doctor Best, Doctor Houssay and Dean MacFarlane.

practical therapeutic project in the Connaught Laboratories. If any of his friends felt doubts, however, of the wisdom of this plurality of interests and responsibilities, their anxiety merely showed their own lack of knowledge concerning Charles Best's capacity for handling such a multiplicity of duties and interests. It was soon clear that he could take them all in his masterful and lengthening stride, and, what was of all things the most important, that promptitude and efficiency in responding to each of these many administrative calls in its proper turn, were not in the least incompatible with a concentration of his thoughts on the further researches, by which he could still make his best contribution to the cause of medical knowledge and of its service to suffering humanity.

If I know Charles Best at all—and I flatter myself that I do know him pretty well—he has in a high degree that special qualification of a real leader in research, that he feels, with a genuine conviction, that those who are associated with him, in different aspects of a common enterprise, not only find his own ideas acceptable, but more commonly seem to anticipate them; so that he has no need to drive or to impose, seldom even to persuade, but can be content occasionally to oil a machinery of collaboration which seems to run of itself. I am confident that he would not wish to impute to his sole personal activity or initiative, any item in the growing and impressive series of important additions to knowledge, in physiology and the related fields of medical research, in which he and his colleagues have been active. I think that he would tell us that one or another of his colleagues has been mainly responsible for this and that special discovery, and that others have made their best contributions by collaboration at various points in the common effort. And I am sure that every member of each of the several teams which he has been leading, would tell us how much they owe to the always active spring of Charles Best's instinct and inspiration, to his sympathetic guidance and his wise judgment. A productive research department is not made by the activity of an individual, however brilliant. A man's power of leadership is shown by the ability of the colleagues who gather round him to work happily with him. You have Departments here, headed but not dominated by Professor Charles Best, in which new and exciting developments, in the field of knowledge which was opened to research by the discovery of insulin, are still being eagerly pursued, and in which clues of comparable interest in many other directions are being followed with the same individual zest and corporate enthusiasm.

A number of us this morning had the privilege of hearing Professor Best give an account, in briefest outline, of some of these many trails which the many workers in these two Departments are following. To seize, in passing, out of a whole range of clues of comparable interest, two which caught my notice, we heard about and saw pictures of the widespread and deep arterial degeneration caused in a young animal by a diet deficient in choline, given for only a few weeks; and we heard more about the more recent and surprising development of knowledge about insulin itself, showing that, in the absence of the pituitary body, insulin can act as a growth-producing hormone. More than the content of all the various researches, however, is the happy atmosphere, as of a large and united family, which so obviously permeates these Departments, and which only the best kind of scientific leadership can create. It unites in common loyalty and a cooperative enthusiasm, men who have grown up here in the Department, scientific sons and even grandsons of the leader, and distinguished investigators from many other countries, who have been attracted here by the reputation of these Departments, and the opportunities which they already afford. These are Departments already of great achievements; and the assured prospect of their expanding activity is such as to justify, even to require, all the resources that a great new Institute can offer; and it is with a feeling of pride and confidence that I invite this distinguished assembly now to take part in the dedication of the new Institute of Physiology, the name of which will perpetuate the great work and the brilliant leadership of Charles Herbert Best.

Sir Henry Dale turns the Golden Key to open the new Institute officially as Doctor Best looks on.

The Opening of The Charles H. Best Institute

At the conclusion of the convocation ceremony, the members of the academic procession and other guests proceeded to The Charles H. Best Institute, located nearby at 114 College Street, where the opening ceremonies were held.

Col. Eric Phillips, Chairman of the Board of Governors of the University, made the following remarks:

May I extend to all who are here today a warm welcome on behalf of the Board of Governors, indeed of the whole University.

We are proud that so many distinguished guests from far and near have seen fit to join us in doing honour to Doctor Best and his colleagues, whose genius is one of our most valued treasures.

In naming this building "The Charles H. Best Institute of Physiology," the Board of Governors intend to pay tribute at the same time to the memory of Sir Frederick Banting in whose debt we shall ever remain.

This building stands as no easy symbol of mere construction skills. It has been a long held dream of Doctor Best and his colleagues in the Faculty of Medicine.

The Board of Governors recognize in the presence here today of so many distinguished scientists a confirmation, indeed a justification, of our long struggle to find funds to provide this new weapon against disease

and to deliver it into the competent hands of our trusted friend, Doctor Best.

I now ask Bishop Hallam to offer a prayer of dedication.

*The prayer of dedication was delivered as follows by the Right Rev. Bishop W. T. Hallam.**

Prayer of Dedication

Almighty God, Father of all mercies, the Source of light and life, and Who art Thyself the ground of our beseeching, we yield Thee hearty thanks that Thou hast put it into the minds of men to erect and to establish this Institute set apart for the healing ministry to mankind.

And especially do we have in remembrance the benefits already manifest from the achievements of Thy servants which have made clear the necessity of this house. We thank Thee for their singular devotion and unflagging pursuit in their quest that the world may yield its secrets for the enlargement of life.

We dedicate this building to the high purpose of the service of men in the relief of suffering and the lengthening of days that they may be the more enabled to address themselves without handicap to the tasks of life in increasing confidence and cooperation according to Thy will.

And we beseech Thee that always in the minds of him who directs and of those who labour with him there may be the dominant desire to work together with an eye single to the advancement of their endeavour and to give themselves to serve Thee and their fellows in sincerity and truth. May Thy Spirit which is in all created things inspire them to think Thy thoughts after Thee and to uncover Thy provision for the welfare of Thy children.

All this we ask in the name of Him who came that men might have life and have it more abundantly, even Thy Son, Jesus Christ our Lord.

Amen.

Col. Eric Phillips: I now have great pleasure in asking Sir Henry Dale to perform the opening ceremony.

Brig. Eric Haldenby: Sir Henry, on behalf of the architects of this building, I have much pleasure in presenting you with the gold key to open the main entrance to the building, *The Charles H. Best Institute.*

Sir Henry Hallett Dale: Mr. Chairman, my Lord Bishop, Mr. President, Brigadier Haldenby: It is for me a privilege, and a great one, that I am allowed to have the honor of opening the building which will mean so much to my dear friend, Charles Best, and his devoted colleagues, and so much for the happiness of the whole world.

Sir Henry Dale unlocked the door and opened the building. In the entrance hallway, a portrait was presented to Professor Best by Dean J. A. MacFarlane.

Dean J. A. MacFarlane: On this happy occasion of the opening of a building to be called The Charles H. Best Institute, I am asking you to pause for a few minutes while I unveil a portrait of Professor Best, executed by one of our great Canadian portrait painters, Mr. Cleeve Horne. The painting of the picture has been made possible by Professor Best's colleagues, students and friends. It will, I hope, in some measure signify to him, and indeed to all those who view it, something of what his name and his example mean to the medical school of this University. We hope it will remind him in the years to come—and we trust they will be many—of the esteem in which he is held by his fellows in this school; and of the gratitude of his students in this and many other lands for his help, encouragement and leadership in research.

I would therefore ask you, Professor Best, to accept this painting from those who have known you—some of us even when you yourself were a student—others who have worked with you as colleagues, but particularly from that steadily growing number of young men and women who have sat at your feet as students, who have been inspired by your genius, compelled by your industry and orderly thinking, comforted and encouraged by your patience and tolerance.

Professor C. H. Best: I am very happy to receive this painting at your hands, Mr. Dean, and I appreciate your kind remarks more than I can tell you. Our association and friendship extends over more than thirty years and it gives all the members of my family great pleasure to have you represent our friends who are making this gift. My wife and I enjoyed the evenings—some fourteen, I think—which we spent with Cleeve and Jean Horne and we have all become very good friends. I gather that this portrait is, for the moment, mine. I would like to present it to my wife—but she will not take it home! We are both very proud to have it hang in this fine building for which it was intended. I trust that there will be an opportunity for me more appropriately to thank all of you who have so kindly and thoughtfully made this presentation possible.

**Bishop Hallam married in 1904 his classmate at Dalhousie University, Lillian Best, the youngest sister of Dr. H. H. Best. Dr. Charles H. Best made his home for several years in Toronto with his aunt and uncle and was living with them during the insulin investigations.*

TESTIMONIAL DINNER TO DOCTOR BEST

Welcome by the President

President Smith:

On behalf of the University, I express to all of you a warm and a cordial welcome. Each of you is a special guest under this our rooftree.

Today has been a happy day for us of the University. In the first place, we have added to our Honour Roll five distinguished scientists who hail from the United Kingdom, the United States, Argentina, and Canada. This gathering together of medical scientists from near and far is a manifestation of the world-wide sovereignty of learning that does not brook boundaries, tariffs, embargoes, quotas or vetoes.

Without discounting but indeed asserting the pre-eminence of these five gentlemen, I declare that their pre-eminence is rooted in their eagerness and their talent to build on the work of others of many ages, climes and lands. And I would assure them that we of the University of Toronto will ever regard them as belonging in a measure to us and will shine in their reflected glory.

In the second place, this is a happy day for us in that (to invoke a Presidential platitude which, I assert, is nevertheless true) we have reached a new milestone, we are entering a new era. We have acquired new facilities for extending the frontiers of knowledge for the betterment of mankind. There is a danger in that reflection, because we might be thereby lulled into thinking that a new building with excellent equipment is an end in itself. It is not. It is only a means whereby outstanding men and women may better perform their tasks for humanity. Men and women who in humility and indeed with reverence will seek to wrest further secrets from Nature. Men and women modest in success and courageous in failure. Men and women who are not clock-watchers. Men and women who will go the second mile. Men and women who will reconcile the dilemma of the irresistible force meeting the immovable mass, and thus produce unforeseen scientific results. Men and women who will inspire talented youth to carry on the work for the alleviation of distress and disease. Men and women with a fervour and a passion for search and research.

There is more than a happy coincidence in the name of our new building, the Best Building. It is truly the Best Building in terms of its recognition of a member of the staff in whom we take great pride. We think tonight of four illustrious names, forever joined in the story of the University of Toronto and in the history of medical research, Banting, Best, Collip and Macleod.

In life and in death, Sir Frederick Banting gave of his utmost, even to life itself, in the service of his fellowmen. Today we signalized by the opening of a building, a twin of the Banting Institute, our appreciation of and admiration for Charles H. Best, and I take this opportunity, Dr. Best, to say on behalf of the University that we think above all of your scientific integrity, your imagination, your power, your capacity to cooperate and to lead, and particularly of your genius in teaching and inspiring young co-workers. In saluting Charlie Best, we think also of Margaret Best, his charming and devoted helpmeet. At this point I am going to pause to afford an opportunity of presenting to Margaret a token of our appreciation of the better half of the Best family.

(Presentation of flowers to Mrs. Best.)

It is particularly fitting, on this occasion, that Dr. Charles Herbert Best should propose the toast to the good health of our guests.

Toast to the Honoured Guests

Dr. Best:

Your kind invitation, Mr. President, to propose a toast to our honoured guests and their wives, gives me the opportunity to thank our University for this realization of hopes. The members of our staff—Drs. Haist, Sellers, Campbell, Fidlar, Markowitz, Monkhouse and Clarke in Physiology, and Drs. Lucas, Franks, Hartroft, Baer, Wrenshall, Rappaport and Campbell Cowan in Medical Research, join me in deep appreciation of the efforts of Colonel Eric Phillips, and the members of The Board of Governors. I would mention particularly Mr. O. D. Vaughan, Chairman of the Property Committee. We will always remember with deep gratitude the many vigorous, essential and kindly steps which you, Mr. President, and you, Dean MacFarlane, have taken in our various crises.

A very large part of the money needed for our new Institute was allocated from the proceeds of the University Campaign for funds. We are indebted, therefore, to the Province of Ontario, to the City of Toronto, to the donors of large and small amounts who made this a success. The equipment for our building has been provided from a Dominion-Provincial Health Grant and my personal indebtedness to the Minister of Health of this Province, the Hon. Mackinnon Phillips, and to the Hon. Paul Martin, the Minister of Health of Canada, is very great. Indeed, I may mention here with deep appreciation, the personal interest of the Rt. Hon. Louis St. Laurent, Prime Minister of Canada. I would like to thank also, Dr. Donald Cameron, the Deputy Minister of Health, Ottawa, and Dr. John Phair, the Deputy Minister of Health of Ontario and Dr. Gordon Brown and Mr. William N. Nichols of the Ontario Department of Health. One section of our building will be devoted to medical aspects of Defence problems and this part has been financed and equipped by the Defence Research Board of Canada, whose Chairman is my former pupil, close friend and colleague, Dr. O. M. Solandt. To some of you from other countries, this may sound in large part like an obligatory recitation of the names of officials, but it is not. These men who have helped us so much, are all close personal friends, many of very long standing. They have a full and sympathetic appreciation of what we hope to accomplish and on this pleasant basis, we have worked together to reach our goal.

The list of private donors is long and I can not mention them individually. We are very sorry that the Hon. Cairine Wilson, the first woman to be a Canadian Senator (and a very close friend of my wife's since the latter's childhood in St. Andrews-by-the-Sea) could not have been here this evening. We owe a very special debt of gratitude to Eli Lilly and Company for their constant interest and more than generous support. I have paid tribute many times to this fine firm, the staff of which we have known intimately since 1922. It gives my wife and me very great pleasure to have our friends Mr. Eli Lilly and Dr. G. H. A. Clowes here and we welcome and thank them. We are very happy that Dr. and Mrs. Bruce Peck are also able to be here and sorry that Mr. George Walden could not come.

The Burroughs Wellcome Co. (United States) has, through its Director, Mr. William N. Creasy, made a generous gift toward a special part of our new Institute and it has thus reflected the interest in our work taken by the parent Company in England, and the Board of Trustees of The Wellcome Foundation, of which Sir Henry Dale is Chairman.

This has been a great day for all members of our staff who will work in this new building—certainly a very great day for the Best family. If you will forgive me, I may say, in the presence of so many close friends, that the first Best in Canada came from near Ventnor in the Isle of Wight. He arrived with Cornwallis, as an officer in the British Army, for the founding of Halifax, Nova Scotia in 1749. All my ancestors for six generations have been Nova Scotians. My early years were spent in West Pembroke, Maine, where my father was the general practitioner. He took his patients to St. Stephen, New Brunswick, Canada, for hospital treatment. I will resist the temptation to describe the charms of Passamaquoddy Bay, on the shores of which both my wife and I were born (St. Andrews, New Brunswick and West Pembroke, Maine). It has a very special place in our hearts and we return to our Schooner Cove Farm whenever we can manage it. We are assisted in ignoring the International Boundary by our close friends on both sides of the border.

The first Mahon came to Canada in 1761 from Londonderry, Ireland and founded Londonderry and Great Village, Nova Scotia. My wife's father, Alexander

Mahon, graduated from Dalhousie, Pine Hill and Princeton. He married Flora Macleod of Prince Edward Island, whose ancestors, of course, came from Skye. Margaret Mahon graduated from the University of Toronto (University College). She began in the General Course but, obtaining honours, entered Political Economy and intended to become a lawyer. She would undoubtedly have been a bencher at Osgoode Hall—or better perhaps, Mr. President, a member of our Faculty of Law! The Law's loss has been my gain. She has been the inspiration and centre of all our activities since 1920 and in addition, has managed to continue her systematic reading and to act as a recorder of all our experiences. Her records and diary of 1920-22 are, perhaps, of special interest and she has been asked by two great publishing firms to make them available. A book might be published under the title: "An Autobiography of a Physiologist by His Wife." We have visited many countries and since the war have flown some 120,000 miles together—mostly in the summer vacation, Mr. President!—and we could write a book under the title: "There are thoughtful and kind people everywhere." It is much more likely, however, that these records will be kept for those for whom they were written—our sons. Margaret Mahon Best was ill at the laying of the corner-stone of our Institute but, as you can see, is very happy and well this evening.

I would like to mention at this time the names of the two men who, in 1938 when I was seriously considering a move to England, recommended to The Board of Governors of The University of Toronto, that our Institute be built. They were: Frederick Grant Banting and John Gerald FitzGerald.

The University, of course, wishes to honour all its guests this evening but some have come to take part in the Scientific Proceedings which are a part of this occasion, and President Smith will permit me to mention them particularly in this toast.

Dr. E. D. Adrian, O.M., President of the Royal Society of London, Master of Trinity College, Cambridge, Nobel Laureate, and this year's Banting Lecturer in our University, is a central figure in scientific research in the Commonwealth and one of the world's leading contributors to medical knowledge. There is a great deal I could say but I must admit that your name, Dr. Adrian, frequently conjures up for me, not the Presidential Chair of the Royal Society, or the Mace presented by Charles II, but a small cabin on the "Bergensfjord" which you and I shared with Sir Henry Dale and Dr. D. Y. Solandt in a war-time crossing of the Atlantic. This picture now merges with one formed by a happy but too short sojourn in a log cabin in the Laurentians, which I know our wives enjoyed as much as we did.

Dr. Detlev W. Bronk, a close friend of a quarter of a century's standing, as President of The National Academy of Sciences, U.S.A., occupies the central position in science in that friendly country which has such tremendous capacity and responsibilities. Johns Hopkins has been fortunate to have him for some five years but he has now succumbed again to his real scientific love and will lead his country in biophysical and medical research as Director of The Rockefeller Institute. The tributes paid to you, Det, by a physician—Dr. Ray Farquharson—and by a surgeon—Dr. J. A. MacFarlane—have a sound physiological foundation! I could say a lot more about you and your wife but will just thank you for your eloquent and deeply appreciated references to Margaret and me at the President's luncheon today.

Sir Henry Dale, O.M., G.B.E., Nobel Laureate, Past President of the Royal Society, one-time Director of The National Institute for Medical Research, of The Royal Institution, and of many other great British Institutions, presents to me an impossible problem—an adequate brief introduction. I visualize him singing the scale to determine the speed of his centrifuge in his very famous and productive laboratory, operating with me on a hot day in Indianapolis in 1922, and under many, many other interesting circumstances. He was chosen to be the central figure in the opening ceremonies of our Institute. I will merely say that I have found him, over a period of 30 years, the best informed, the most kindly and understanding, and the most stimulating friend and mentor whom I have had. I thank him for his kindness in opening our Institute and my wife and I thank Lady Dale and Sir Henry for more happy times than we can ever mention.

Professor Joseph P. Hoet, Head of the Department of Medicine, University of Louvain, is an outstanding clinical investigator of Belgium. He was the originator of the plan for a Federation of the Diabetics of the World. Last evening he was honoured by The Canadian Diabetic Association when they made him an Honorary Life Member of the Society. Dr. Hoet and his wife—whom we are so delighted to have here tonight—have been warm personal friends since student days in London. Now, all "the family Hoet," including seven splendid children and one beautiful granddaughter, aged one year, are known affectionately by each member of our family.

Dr. Elliott P. Joslin, the Dean of all those who treat diabetes, is a physician who has been an example to

thousands of others and a doctor to hundreds of diabetic physicians. My aunt was a nurse-in-training in the same hospital in Boston when he was a Houseman. Later, when she developed diabetes she became his patient. She talked about Dr. Joslin to me long before I entered the University of Toronto. I lectured for Dr. Joslin at Harvard University, with President Elliott in the Chair, thirty-one years ago. Dr. Joslin ranks very, very high in my private list of American citizens. Mrs. Joslin and his daughter-in-law, Mrs. Allen Joslin, have been able to accompany him on this occasion and this is a source of particular pleasure to us all.

Professor B. C. P. Jansen—so well-known throughout the scientific world for his isolation of Vitamin B_1 from rice polishings—is head of Biochemistry in the University of Amsterdam. We are very glad to have Mrs. Jansen and you here tonight, Sir, and remember with pleasure your hospitality in The Netherlands and your sojourn immediately after the war, in our Department.

Dr. Robin Lawrence—because he has done so much for others Dr. Joslin has called him the outstanding living diabetic. He is a renowned clinical investigator, founder of the first organization of diabetics in the world, President of The International Federation of Diabetics. He has been and is a wonderful friend. He is the fourth of my very close friends who has sent a son to work for a year or more with me. The others are Professor Donald Fraser, Professor Arthur Colwell and Dr. G. H. A. Clowes. This has been a great responsibility for us all but it has worked very well, I think, in this small series of experiments. I admit the absence of adequate controls.

It is a pleasure to welcome one of our Danish friends, Professor Einar Lundsgaard, the distinguished Head of Physiology in Copenhagen. He was the President of the very successful XVIII International Physiological Congress in Copenhagen in 1950.

Mr. and Mrs. Merrill Muttart of Edmonton, Alberta —we are indebted to them for many things. Recently they have presented us with a beautiful painting by Gissing, to be hung in the new Institute, and with flowers for this occasion flown in from the Hawaiian Islands.

Dr. Bernardo Houssay—Nobel Laureate, outstanding and courageous leader of medical science in South America, is certainly one of the greatest physiologists of our world. He is a warm personal friend and was our charming host, with Mrs. Houssay, for a month in Buenos Aires.

Dr. Wilder Penfield, O.M., F.R.S., I endorse and would extend if I could, what my close friends Dr. Farquharson and Dean MacFarlane have said about you today, Wilder. In Canada we are all very proud of the position you have won as an outstanding international figure in brain surgery, clinical investigation and neurophysiology. Mrs. Penfield and you were extremely kind to many of us in Montreal during the International Physiological Congress and we hope that in the years to come our paths will merge very frequently.

Sir Rudolf Peters, F.R.S., a world-renowned biochemist, is Head of that Department at Oxford. He is the discoverer of British anti-lewisite, a vitally important substance in war and peace. It has given us particular pleasure to see Sir Rudolf and Lady Peters in Montreal, in the Laurentians and now in Toronto.

Professor and Mrs. Philip A. Shaffer. Dr. Shaffer is a very renowned biochemist and an old friend, from Washington University, St. Louis. I will always remember the first time he met my wife. It was over 25 years ago in Washington. We decided not to attend an evening meeting of the Federated Societies but to go for a long walk. When we returned we met Professor Shaffer and I introduced him to my wife. She immediately said that we had had a nice walk and had felt that we might have been bored if we attended the meeting. "You would certainly have been, Mrs. Best," said Professor Shaffer, with his courtly bow, "I was the speaker of the evening." They have been firm friends ever since.

The President of The National Research Council of Canada, Dr. E. W. R. Steacie, F.R.S., is internationally famous for his contributions to chemistry. A fine scientist himself, he now gives leadership to all scientists in Canada. He honoured our International Physiological Congress by his presence last week in Montreal and we are proud to have him at our opening ceremonies here today.

The American Diabetes Association is represented by its Second Vice President, Dr. Henry Ricketts, the distinguished son of a famous father. Many of you know that the rickettsial diseases were named to honour Dr. Ricketts' father who succumbed to one of these maladies while investigating it. The Editor of DIABETES, Dr. Frank N. Allan (and Mrs. Allan) is here. He has brought fame to his Alma Mater, the University of Toronto and was President of the American Diabetes Association last year. The efficient Executive Director of the American Diabetes Association, Mr. Dick Connelly, is also a very welcome guest.

Sir Lionel Whitby, M.C., M.D., F.R.C.P., eminent pathologist and haematologist, who brilliantly directed the war-time efforts on blood preservation and distribu-

tion for the Commonwealth Forces. Vice Chancellor of Cambridge University, Master of Downing College, and Regius Professor of Physic. We all thank him for his exceptionally fine address this afternoon. I will always remember, Sir Lionel and Lady Whitby, your kindly offer of a home in Cambridge at Downing College.

We are indebted to the architects, Mr. Mathers and Mr. Haldenby and to their Mr. Murphy who has worked so well with our Mr. Campbell Cowan and with our most interested and helpful Superintendents, Colonel LePan and Mr. Dean Maxwell. It is a pleasure to have the distinguished artist Mr. Cleeve Horne with us this evening, and my uncle The Rt. Rev. Bishop Hallam in whose home I lived throughout the insulin investigations in 1921 and 1922.

It is possible, Mr. President, to mention only a few more of our honored guests by name. The Deans of our Medical Faculties: Dean Collip (I would pay again my tribute to Dr. Collip for his brilliant work on insulin, parathormone, ACTH and many other aspects of endocrinology and for his great contribution to medical research in Canada as Director of the N.R.C. Division of Medical Research), Dean Ettinger, Dean Bell, Dean Richard, and my opposite numbers in Physiology: Professors Dugal, Robillard, Stevenson, and Professor Louis Jaques of Saskatoon who has been a very special colleague and friend.

The members of my staff, Mr. President—and I would mention particularly Professor Haist, who has carried so much of the load of the planning and arrangements for these celebrations—our esteemed Dean, and my distinguished colleagues in our most friendly Faculty of Medicine of this University will, I know, join with me in proposing this Toast—The Health of Our Honoured Guests.

Tributes to Doctor Best

Tributes to Dr. Charles H. Best's distinguished career as a scientist and co-discoverer of insulin were paid by a group of noted scientists at the dinner in Hart House following the formal opening of The Charles H. Best Institute. Speakers were introduced by Sidney E. Smith, President of the University of Toronto.

President Smith:

Dr. Elliott Proctor Joslin. Harvard and Boston—how much these names suggest in themselves! What pictures are thrown on the screen of the mind! But Dr. Joslin has earned for himself one of the highest titles, 'a Great Physician.'

Dr. Joslin:

Toronto and Boston! Long before I knew Charley Best I came to Toronto, to Hart House, and in Hart House I saw a vision for the Vanderbilt Dormitory in Harvard. Therefore it is peculiarly appropriate for me to say that a direct outflow from this wonderful, beautiful and useful building was the Vanderbilt Dormitory.

But there is another thing which touched me, because in the Vanderbilt Dormitory we have the Charles H. Best Room where the students gather. We have that Charles H. Best Room to inspire the students because, as was said at the dedication of the dormitory, when Charley Best, then just at the beginning of his medical career, joined in the discovery of insulin, *ipso facto* he changed the status of medical students in the world from tnat of students to that of investigators.

Dr. Banting first came down to talk to us, and later Dr. Best. I remember well the meeting when Dr. Best spoke before all the students at Harvard and how they leaned over the railing at the back. President Elliott, then quite old, came over because he wanted to hear that young student talk. I was interrupted in the meeting and was quite annoyed when someone gave me a telegram, and while I can't quote you the whole of it, that was the one in which Dr. Banting said that in any meeting or occasion when there was a large gathering, we were to say, about the Nobel prize, that he would share it with Charley Best. And how delighted we all were! It worked out so well. Dr. Banting shared it with Dr. Best and Dr. Macleod with Dr. Collip. That was a delight and characteristic of both of the recipients. Sir, we remember those occasions.

We knew diabetics for a quarter of a century before insulin was discovered. No one here can realize what insulin has done to diabetics and what it has done for all doctors as well, and what you, Sir, have done

for medical students.

Thank you for including me among all these notable scientists who received degrees today. I appreciate the honor, and realize that it has come to me for a different reason.

President Smith:

Dr. Bernardo Alberto Houssay. The scientific herald of South America, and Nobel Prizeman. It is a pleasure to have you here, Dr. Houssay.

Doctor Houssay:

It is indeed a privilege and a pleasure to speak this evening in representation of Latin American biologists and doctors, in order to express our admiration for Dr. Charles Best, for his outstanding human qualities and his magnificent achievements in science in the course of a hard-working and fruitful life.

His discovery of insulin, in collaboration with Banting, brought him world-wide fame at a very early age. Since then, he has become a great master of physiology, teaching it personally in Toronto and, by means of his book, throughout the world. He has organized and led a brilliant group of scientists who have made contributions of the greatest importance to knowledge. Amongst these the work on fatty liver and the role of lipotropic and anti-lipotropic factors and of choline, should be mentioned. He also made the pioneer studies on the use of anticoagulating substances in the treatment of thrombosis and infarction. By his discovery of insulin and of the factors which protect the liver and kidneys, Dr. Best has earned the right to be considered one of the greatest benefactors of mankind.

Dr. Best adds to his eminent qualities as a scientist and teacher a charming personality which has endeared him to all who have had the good fortune to know him.

I am here to express the best wishes of Latin American scientists to Professor Best for a long, prosperous and happy life, and our hopes that the Institute which from now on bears his name will flourish with increasing strength throughout the ages for the glory of Toronto and of Canada, and for the welfare of humanity.

President Smith:

Dr. Joseph P. Hoet is a distinguished clinician and scientist. He is Professor of Medicine at that ancient and renowned foundation, the University of Louvain. Dr. Hoet.

Dr. Hoet:

I have been charged by the Royal Academy of Medicine of Belgium to leave an address with you, Mr. President, for Professor Best, and with it to convey to Mrs. Best the greetings of her good friends in Belgium. Also, I have like pleasure in bringing an address from the University of Louvain to Dr. Charles Herbert Best. These addresses have been sent to Professor Best, a very great Canadian, in recognition of his service to mankind. It is fitting that now there is an Institute in which succeeding generations can continue the advance of medical science, made possible and stimulated by the success of this great investigator.

I thought about what I could do to show my friends, Charley and Margaret Best, how much I appreciated being able to join in their joy in the magnificent ceremonies today. I prepared for them a reprint which I obtained from the grandson of Pasteur. Just before the catastrophe of 1870, Louis Pasteur wrote three memoranda about applied science, in which he dealt with the purpose of science. There is no applied science without science. By a remarkable coincidence this is the same paper that Dr. Bronk quoted today. There is on the cover the imprint of the Hotel de Ville of Louvain. I have included also a brief story of Pasteur and what he did for science. This reprint I have brought to give to my good friend, Charley Best, to show that he had to have a laboratory in which to work, not just to teach.

"When the physicians and the chemists leave their laboratories, when the biologists neglect their collections and their explorations, they become incapable of any discoveries.

"The most valuable ideas, the most logical speculations, will only come to have a body and soul when confirmed by observation and experiment. Laboratories and discoveries are terms which are related. Deprived of laboratories, the physical sciences will become the image of sterility and dull. Limited and impotent they will only be sciences for teaching and not sciences for progress and of the future. Give them laboratories and there will return life, productivity and strength.

"If you are concerned about the part that your country can play in the extension of these wonders, I beg you to give your attention to these sacred institutions designated by the expressive term of "laboratories." Ask that they be multiplied and that they be equipped; they are the temples of the future, of wealth and prosperity. It is there that humanity is enriched, strengthened and improved. One sees in the works of nature, works of progress and universal harmony, while the works of humanity itself are too often those of barbarism, of fanaticism and of destruction."

Greetings from Belgium

Addresses were presented to Doctor Best by Dr. Joseph Hoet on behalf of the University of Louvain and the Royal Academy of Medicine of Belgium.

The Catholic University of Louvain heartily congratulates Professor Charles Herbert Best, on the celebration of more than thirty years of successful and intensified work, since the discovery of insulin, in the Connaught Laboratories and in the Banting and Best Department of Medical Research, and on the solemn inauguration of The Charles H. Best Institute for Medical Research.

Remembering his promotion to the Honorary Degree of the Faculty of Medicine of Louvain, the University still more admires the efficient work of the great scientist who throughout his whole life has presented a splendid example of high culture in the service of humanity and of entire devotion to suffering men, "striving to do his whole duty by his neighbor," so that "mankind is in some degree better because he lived and fulfilled his task."

For this benefactor of humanity the Catholic University of Louvain prays God that he may for years know further success in his research work.

Louvain, September the 15th, 1953.

Msgr. van Wayenbergh

To Prof. Charles H. Best, honorary foreign member of the Royal Academy of Medicine of Belgium:

The Royal Academy of Medicine of Belgium was informed during its meeting today that a Medical Research Institute will be dedicated in Toronto to honor you and your work on September 15, 1953.

"It gives us strong satisfaction and pleasure to take this opportunity to express again the feeling of admiration and interest which we had the honor to present to you when you gave an address here on July 12, 1947. It conveys the thoughts of millions of human beings who are indebted to you for recovery of health and the joy of living.

"Certain of the participation of your own feeling, the Academy recalls at the same time the memory of Professor Banting, your illustrious compatriot and associate in your scientific work. Professor Banting was also one of the most distinguished honorary foreign members of this Society.

"The Academy is assured that the Institute established in your honor will render numerous and important contributions to humanity. It hopes sincerely that these contributions will be productive and enduring.

"The Academy wishes to express again to you, personally, and to the scientific workers of your country, great friend of our own, its most cordial greetings and best wishes."

In the name of the Academy,
Prof. N. Wattiez, President
Prof. R. Bruynoghe, Permanent Secretary

President Smith:

Dr. Robin D. Lawrence, of London, England. Philosopher, scientist and author.

Doctor Lawrence:

Charles Best is a man of truth, so even I must believe the kind words he said about me, without any undue reservations. But, of course, I know why I'm here. It is simply because I have had diabetes for a long time, even before insulin, and I'm a perfect, living example of what it can do.

But, dear scientists and other people, let us halt for a minute and consider some of the possibilities that science may bring to diabetics. Here we are, or here am I, surrounded, I suppose, by the highest powered research workers on carbohydrate metabolism and diabetes that can be found in the world. Now, what are they doing? They're all probing, searching, getting on as fast as they can with the cure of diabetes and its prevention. Let us stop for a moment and think what this might mean to diabetics and the world in general.

I suppose the discovery of a cure of diabetes means that insulin will no longer be produced. There are certain aspects and consequences thereof that might arise, to which I will draw your attention for a moment. I was talking to a protein chemist, lately Professor of Biochemistry at Cambridge, not so long ago, and he expressed to me his grave concern lest a cure for diabetes might be found and insulin would not be produced: because, he said to me, "Insulin is the most extraordinary protein in the world. I've devoted my life to it, and goodness me, if diabetes were cured there won't be any insulin to help solve all the problems of protein chemistry."

There's another point of view. All over the world there are being formed, and have been formed, diabetic associations of laymen. Some rich, some poor, some in existence for a long time, some only begun. Well, don't you think it would be wise in the interests of research in general, if a cure for diabetes wasn't found too soon, so that they might accumulate large millions of dollars and pounds for research before the need for insulin disappeared?

There is another little aspect which comes to mind. These long-standing, inured, diehard, never-die diabetics have been putting insulin into themselves for many years (once a day, twice a day, in some impossible places it's being given three or four times a day.) Well, just imagine this wonderful habit we've formed —this discipline which makes us such wonderful people, such wonderful workers, such wonderful, controlled citizens. If that were taken away from us in a hurry I've often asked myself if without insulin, life might not be rather *pointless!*

But enough of flippancy which flows out of me all too readily, sometimes inappropriately, but this is a very serious occasion and I turn over a new leaf from those previous aspects that I have brought to you scientists' attention.

I really have an easy task here tonight. I bring a gift from the world, and it's a very fine one, as you'll see in a minute. I think it's a touching gift and I hope you'll be touched completely. It really is a gift from the I.D.F., the International Diabetes Federation. This is something rather new, and perhaps a word or two about it would not be out of place. Perhaps you know, perhaps you don't, that many countries, twenty to thirty, have formed over the years, national diabetic associations, of laymen mostly, with interested doctors associated with them. It's done a lot of good in many ways, but I needn't go into that. Two or three years ago these formed themselves into an International Diabetes Federation. And now from them—and surely they represent all the diabetics in the world, the lay diabetics of all classes—I bring this gift, Charley Best, to you. It can only be a token, but here it is. It's a silver writing pad, from Holland, where they have taste and discretion, and on the outside of it is an impression, a dedication:

"To Charles H. Best, and his Institute, from the International Diabetes Federation."

Inside, and this is the important and touching and true thing,

"Thanks for our lives."

When you thank a man for your life, as so many millions are doing through this token, there are no words one can find to say more—

"Thanks for our lives."

And, dear Charley, I don't suppose you are often worried or disturbed, but when you get down to your Institute and things are more puzzling, shall we say, than you expected, or when you're going to raise your next three million dollars, and you've got to scratch your head just a little about that, you can just open this little book and all will be smooth and soft, and you will believe, I hope, that this is a real message, a true message from those who sent it. I'm privileged to give it.

President Smith:

Dr. Edgar Douglas Adrian. Trinity College, Cambridge, Nobel Prize winner, President of the Royal Society, Order of Merit—a singular honor. With Doctor Penfield and Sir Henry Dale, three out of the twenty-four members of the Order are in this room.

Doctor Adrian:

I think all of your guests must be feeling that they are very fortunate people to be invited here tonight. One doesn't have to be a doctor to feel proud of the achievements of science, when we come to a place where a fatal disease has been conquered, and a physiologist can be all the more grateful if he has an opportunity of joining in the celebration.

But before I speak as a physiologist, let me speak more officially on behalf of the Royal Society of London. The names of Banting and Best adorn our Hall of Fellows like those of Jenner and Lister. It's my privilege to bring the greetings of the Royal Society to the University of Toronto and to say that the Society regards it as an honor to be officially represented on this occasion.

Speaking unofficially, I want to add one word by way of a sequel to the picture which Charley Best has painted of our meeting in the cabin on the old Norwegian liner which crossed the Atlantic in 1941. It contained four of us, Sir Henry Dale, Best, Don Solandt and I. It was a rather old and not very well ventilated boat, but Best and Solandt, with true Canadian hospitality, insisted on our taking the better ventilated lower berths while they went up to the top where there was a steam pipe which, I think, connected directly to the main boiler. Fortunately, it wasn't what then would have been considered an eventful voyage, but there was one event which we all, I think, remember. Best referred to it this morning. Soon after we left the Clyde, the captain, hearing that we were a group of scientists, sent someone to the cabin to ask if any of us knew any biochemistry. So, Dale said he had a man named Best who might know something about it. Best went along to the captain, and it transpired that the captain had diabetes, and wasn't very happy about the dose of insulin he was taking. When he found that he had the foremost authority in the world on board, he was naturally enormously relieved to get advice, and you can imagine that our party gained the most privileges it was possible to gain. I remembered it because it did bring

home the real benefits which have come to so many sick people from Banting and Best's work. At that time I suppose most people in most parts of the world were thinking up new ways of killing one another, and it was an agreeable change then to be reminded that science could be put to other uses. We've been reminded of that this afternoon and this evening, and we're very grateful to the University of Toronto for giving us this exceedingly pleasant and timely reminder. Thank you.

President Smith:

Dr. E. W. R. Steacie. President of the National Research Council. Last but not least. It is good logic, good mathematics and therefore true, that there is no "least" in this group of respondents. When we think of Dr. Steacie we think of Ottawa and McGill—a potent conjunction. He has been a strong and benign leader of Canada's scientific endeavors. On behalf of Canadian universities, we thank him for past favours and at the same time, solicit future patronage.

Doctor Steacie:

I find myself tonight as the lone sheep amongst a pack of medical wolves.

It would be very much out of place for me to discuss Dr. Best's scientific achievements—these have been dealt with authoritatively already. But there is one aspect of Dr. Best's career with which I have personal connection through the Research Council, that I can speak about. We had been charged, through the war, with advice to the services and with medical research, and before the war, through the war, and since, with the giving of grants and scholarships to assist medical research. I think this program has been successful because we have been able to get the advice, the help, the hard work of a very distinguished group of Canadian medical people—to mention only a few, there are Banting, Best, Collip, Penfield, and many others. Because of this I think a great service has been done to Canadian medicine. We feel very proud of the way in which our medical advisers have handled medical affairs, and no one has done this better than Dr. Best.

Now it may come as a shock to you, Mr. President, to realize that Dr. Best has spent considerable time thinking about giving money to other people. (I'm sure it has never struck you that his thoughts were not along those lines.) But in this connection, over the years, Dr. Best has rendered very great service through his work on Naval Medical Research and through his work on the Advisory Committee on Medical Research of the National Research Council. I think this is just one of the many ways, apart from his scientific achievements, in which he has laboured for the general welfare of medical research in Canada, and for the welfare of medical research workers. I would like to pay a tribute to him, as a non-medical man, from this point of view where I really have personal knowledge of how much we owe him. Thank you.

The Distribution of Alloxan in the Rat

Bernard R. Landau, Ph.D., and Albert E. Renold, M.D., Boston*

Several theories have been proposed to explain the diabetogenic action of alloxan. Some of these depend upon a selective accumulation of this compound in the beta cells of the islets of Langerhans. Determinations of the concentration of alloxan in the tissues of the rat, most recently employing alloxan labeled with the nitrogen isotype (N^{15}) or carbon (C^{14}) [1, 2] have shown that, after intravenous injection, the concentration of alloxan in the pancreas is no greater than in other tissues, such as the kidney, liver, lung and spleen.

Analyses of the whole pancreas for its alloxan content, however, can not reveal the amount of alloxan which has entered the pancreatic islets, since these constitute only a small fraction of the total weight of the pancreas. By means of autoradiographs we have been able to determine to some extent the microscopic distribution of radioactive alloxan in rat tissues.

EXPERIMENTAL WORK

Rats of the Wistar strain, raised in our own colony, were used. Alloxan-2-C^{14} monohydrate (specific activity 1.3 μc. per mg.) was injected intravenously after a 24-hour fast. The alloxan-2-C^{14} was prepared from urea-C^{14} by small scale modification of the methods previously described [3, 4]. Five minutes after injection the animals were killed, exsanguinated and samples of pancreas, kidney, liver, spleen and stomach were quickly removed and frozen in isopentane at -170° C. These tissues were then dehydrated, sectioned and autoradiographed by the method of Holt and Warren [5†].

RESULTS

The administration of normal diabetogenic doses of alloxan was first investigated. However, when a rat weighing 270 gm. was given 50 mg. per kg. of radioactive alloxan intravenously, the resulting tissue activity was insufficient, even after a 6-months exposure, to give satisfactory autographs of any tissue but the kidney. The experiment was therefore repeated using higher doses and smaller rats. A dose of 22 mg. was given to each of three rats weighing between 40 and 75 gm. (290 to 550 mg. per kg.). After an exposure of 6 weeks, the autographs were developed. The results were similar in all three animals.

Figure 1a shows a magnification of a section of the pancreas obtained from one of these animals and Figure 1b is the corresponding autoradiograph. It shows greater concentration of radioactivity in the supporting connective tissue and islets than in the acinar tissue. A section of kidney is shown in Figure 2, a and b, and demonstrates high concentration in the region of the tubular elements of the cortex. Sections of the liver, lung and spleen showed apparently uniform distribution throughout the tissues, though the concentrations appeared to be as high or higher than that in the islets of the pancreas. Figure 3, a and b, a section from the antrum of the stomach, shows a high concentration in the submucous layer.

After a 9-months exposure, an autoradiograph of a section of pancreas of a rat given a normal diabetogenic dose of alloxan was obtained, Figure 4, a and b, and demonstrated a distribution of isotope similar to that

This study was supported in part by the United States Atomic Energy Commission.

* Postdoctoral Fellow of the United States Public Health Service, 1951-1953.

Address communications to Doctor Landau, Department of Biological Chemistry, Harvard Medical School, Boston 15, Mass.

† The authors are greatly indebted to Dr. M. Holt for her assistance and advice in the preparation of these autoradiographs.

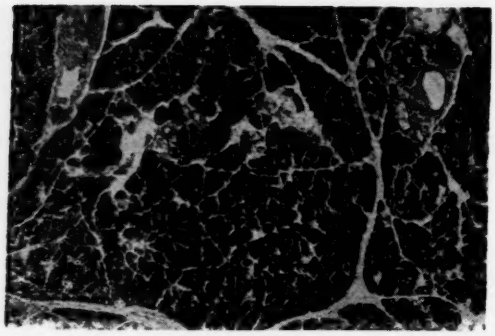


FIGURE 1a. Frozen-dried section of pancreas of a 75-gram rat killed 5 minutes following intravenous injection of 22 mg. of alloxan-2-C^{14} (1.3 μc. per mg.). Embedded in tissuemat; extracted with xylol; 8μ section; hematoxylin and eosin stain; magnification x 60.

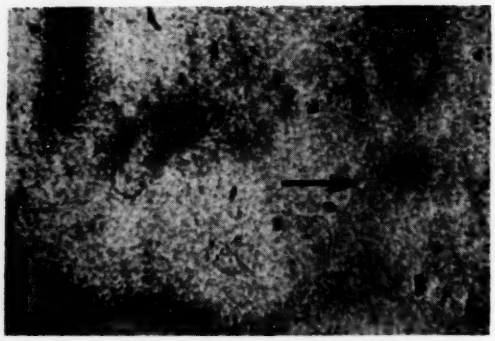


FIGURE 1b. Autograph of the tissue shown in Figure 1a. Prepared with contact method using 10 μ tantalum foil spacers and contrast lantern slides; exposure time 6 weeks. Note the concentration of isotope in the area of the islet indicated by the arrow and in the supporting connective tissue is greater than in the acinar tissue.

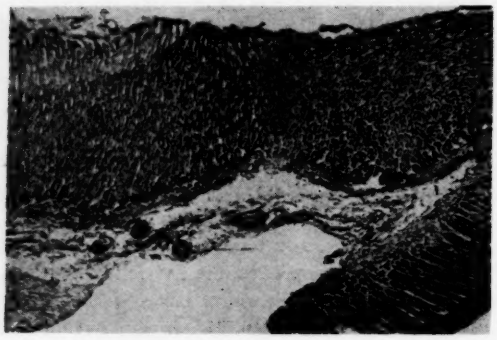


FIGURE 3a. Frozen-dried section from the antrum of the stomach of a 40-gram rat killed 5 minutes following injection of 22 mg. of alloxan-2-C^{14} (1.3 μc. per mg.); magnification x 60.

FIGURE 3b. Autograph of tissue shown in 3a. Note the very high concentration of isotope in the submucosa.

just described for rats receiving higher doses.

DISCUSSION

The distribution of radioactivity observed in our experiment is in good agreement with the relative concentrations of isotope observed by Lee and Stetten[1]. In view of the rapid urinary elimination of the isotope, they attributed its high concentration in the non-protein-nitrogen fraction of the kidney constituents, to products derived from the alloxan in tubular and renal pelvic urine. Our results show a relatively high concentration of activity in the tubules 5 minutes after injection of alloxan. It is in the tubular cells, that necrosis is frequently observed after alloxan administration. The relative concentration of radioactivity in the islets of the pancreas may be attributable to their extensive blood supply. It should be emphasized again that this relative concentration in the pancreatic islets is apparent only in comparison with the surrounding acinar tissue, and not when comparison is made with other tissues such as kidney, liver, lung or spleen. The submucous layer of the stomach contains large blood and lymph vessels and venous plexuses which may account for the high concentration here.

Two mechanisms may be considered to explain the diabetogenic action of alloxan. (1) Selective accumulation of alloxan in the islets in excess of other tissue cells leading to damage of the islets. Such a toxic mechanism has been suggested by Brückmann and Wertheimer[6]. (2) Greater sensitivity of the islet cells as compared to other tissue cells, leading to damage of the islets even without selective accumulation. Such a

FIGURE 2a. Frozen-dried section of kidney of a 40-gram rat killed 5 minutes following intravenous injection of 22 mg. of alloxan-2-C^{14} (1.3 μc. per mg.); magnification x 48.

FIGURE 2b. Autograph of tissue shown in Figure 2a. Note the very high concentration of isotope in the region of the tubular elements of the cortex.

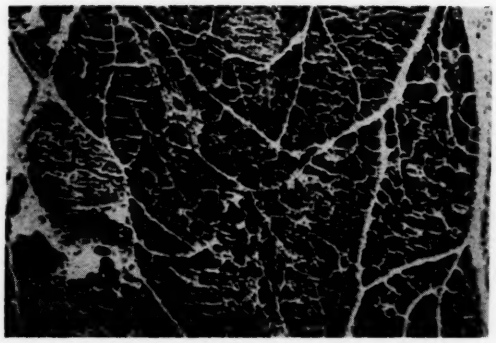


FIGURE 4a. Frozen-dried section of pancreas of a 300-gram rat given a normal diabetogenic dose of alloxan-2-C^{14} and killed one hour following injection; magnification x 64.

FIGURE 4b. Autograph of tissue shown in Figure 4a. Exposure time 9 months. Note the concentration of isotope in the area of the islets indicated by the arrows.

sensitivity might be the result of a specific reaction of alloxan with zinc in the islets as suggested by Kadota[7], or by alloxan inactivation of a sulfhydryl containing enzyme system as suggested by Lazarow[8], or by another as yet unknown mechanism.

We found no greater concentration of alloxan in the islets of the pancreas than in cells of other tissues studied. Our results would seem to support the theory of greater sensitivity of islet cells rather than that of selective accumulation.

SUMMARY

Radioactive alloxan has been injected into rats and their tissues have been autoradiographed.

1. Radioactivity is in higher concentration in the islets and connective tissue of the pancreas than in the surrounding acinar tissue, but not in higher concentration than in kidney, liver, lung or spleen.

2. High radioactivity is found within minutes after injection in the renal tubules, accounting for the large portion of isotope which can be recovered from the kidney as compared to other tissues and possibly for the frequent occurrence of necrosis of tubular cells after alloxan administration.

The authors wish to express their gratitude to Dr. A. Baird Hastings for his guidance and constant encouragement.

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The National Institute of Arthritis and Metabolic Diseases

The National Institute of Arthritis and Metabolic Diseases is one of seven medical research institutes located in Bethesda, a suburb of Washington, D. C. Known collectively as the National Institutes of Health, this organization is the principal research arm of the United States Public Health Service. The Clinical Center will provide each of these institutes with facilities for patient care and for both clinical and laboratory investigation.

In 1950 the 81st Congress of the United States, through Public Law 692, known as the "Omnibus Medical Research Act," provided, among other things, for the establishment of a research institute devoted to the study of arthritis and metabolic diseases.

The Institute thus created within the Public Health Service was charged with primary responsibilities to conduct research in the rheumatic and various metabolic diseases; to assist and foster such research in non-Federal institutions; and to support programs of instruction and training in diagnosis, prevention, treatment and rehabilitation of these disorders.

To meet these responsibilities, the Institute is organized administratively into three major divisions, representing laboratory research, clinical investigations, and extramural programs. The Institute is administered with the help and guidance of a National Advisory Council composed of physicians and laymen representing broad professional and public interests. Appointments to the Council are made by the Surgeon General of the Public Health Service.

The newly organized program of *clinical investigations* will conduct research in rheumatic diseases, mineral and energy metabolism, endocrine disorders, diabetes, nutrition, hematology, and other problems. The Center provides a total of 500 beds distributed approximately as follows among six of the Institutes: 125 to the Cancer Institute, 105 to the Heart Institute, 100 to the Institute of Mental Health, 75 to our Institute, 50 to the Microbiological Institute, and 40 to the Institute of Neurological Diseases and Blindness.

The average teaching and research hospital devotes about twice as much space to patient care as to research. This ratio is reversed in the Clinical Center. Patients are to be admitted solely for clinical investigation and will be subjects for special studies designed in advance. They will be referred from other medical institutions or by physicians in private practice. No fees will be charged, since we feel that by his presence and his cooperation the patient will be contributing as a member of a research team.

The Center will have the usual resources of a modern hospital, including ancillary services such as physical medicine and rehabilitation, medical and psychiatric social work, recreational therapy, and spiritual ministry. The patients' rooms and nursing and medical services are designed to provide maximum comfort to the sick and working convenience to the staff. Because the average stay of many patients will be considerably longer than in most hospitals, there will be a chapel, auditorium, post office, bank, cafeteria, and other such facilities.

A follow-up department will be concerned with patients returning periodically as part of their study and with special studies involving examination of normal controls, ambulatory patients, and similar functions directly related to the research program. An outpatient department, in the usual sense of the term, is not contemplated.

A major objective of modern medicine is to establish relations that will permit an integration of the clinical and laboratory skills of the nation to work productively for the welfare of man. A basic principle that will govern the studies at the Clinical Center is that the welfare of the individual takes precedence over every other consideration. We therefore expect to give each patient the same high quality of medical care that he would receive in any of the best hospitals of the country. The ultimate purpose is to help provide the practicing physicians of this nation, and of the world, with better methods for combating physical suffering and emotional imbalance, for prolonging human life, and for making all the years of man's life more useful both to him and to society.

Abridgment of statement by Dr. Russell M. Wilder in the Bulletin on Rheumatic Diseases, May 1953.

Recent Statistics on Diabetes

The death rate from diabetes up to the end of September 1953 shows divergent trends in various population groups as compared with the corresponding period of 1952. This is evident from Table 1. The provisional data for the United States based upon the 10 per cent sample of death certificates show a very small decline. In contrast, figures for the urban wage-earning population, represented by the Industrial policyholders of the Metropolitan Life Insurance Company, show a sharp rise. Increases are reported likewise in all the States and local areas for which the figures are regularly collected, except in Maryland and Baltimore. The two Canadian cities, Toronto and Montreal, also show an increase in the death rate from diabetes in the first nine months of 1953 over the same period a year earlier.

Figures for the first half of 1952 and of 1953 showed a moderate rise between the two years in the United States, and a somewhat larger rise among the insured group. For the most part, the changes in the rates between the first six months of 1952 and 1953 for the individual areas are somewhat smaller than those recorded for the first nine months.

The rise in diabetes death rates recorded in many areas in 1953 reflects primarily a relatively severe outbreak of respiratory disease earlier in the year and the sustained heat wave that blanketed a great part of the country during late August and early September. Both of these circumstances favor a temporary but significant increase in mortality among persons with chronic disease, and the older persons in the group are particularly affected. It is difficult to understand why the preliminary statistics for the country as a whole for the first nine months showed no increase because the general death rate for the country was higher in this period of the year as compared with 1952; for September alone the increase was 3.4 per cent. Perhaps the failure for an increase in mortality among diabetics to be reflected in the death rate from the disease may be due to normal variations in the 10 per cent sample or to the classification of an unduly large proportion of these deaths under other chronic diseases, particularly the cardiovascular-renal group, or under heat exhaustion.

Figures for England and Wales are available only up through June of 1953. The death rates from diabetes both among males and females for the first six months of the year show a moderate rise from the previous year. This increase was all incurred in the early part of the year, when England also was experiencing the effects of a severe influenza outbreak. In contrast, diabetes mortality in the second quarter was low, and the margin between the two years was considerably reduced by the end of the second quarter. Figures for the first nine months of 1953 for London Administrative County show a decrease in diabetes deaths from the similar period of 1952. This is a distinct reversal of the situation earlier in the year.

Regional data for the United States for the first six months and the first nine months of 1953 are shown in comparison with the figures for corresponding periods of the two preceding years (Table 2). The trends by region between 1952 and 1953 for the first nine months are rather mixed. Moderate increases in rates occurred in the South Atlantic and West South Central areas. Figures for other areas show either relatively modest changes, or the number of deaths is too small to attach much significance to the variations. As compared with two years ago, there has been a significantly large decrease in the death rate in New England. In contrast, the adjoining Middle Atlantic States show a rather sizable rise over the same period.

Final data on death rates from diabetes in individual states are now available for 1950. These data together with those for 1949 are given in Table 3. As against a modest decline in the death rate between 1949 and 1950 for the country as a whole, there were sizable reductions in several States, notably, four of the New England States, Illinois, Michigan, South Dakota, West Virginia, Alabama and Montana. On the other hand, Pennsylvania experienced a rather substantial increase in its rate. For the remainder, the changes were either minimal or the number of deaths too small for the variations to be significant.

Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues from Association members and other readers of the Journal.

TABLE 1

Recent data on diabetes mortality—deaths and death rates—first six and first nine months of 1952 and 1953

Area	Death Rates per 100,000				Number of Deaths			
	Jan.-Sept.		Jan.-June		Jan.-Sept.		Jan.-June	
	1953	1952	1953	1952	1953	1952	1953	1952
United States (10% sample)	16.0	16.2	17.0	16.6	1,896	1,877	1,332	1,276
Metropolitan Life Ins. Co.								
Industrial Policyholders	15.4	14.0	15.7	14.4	2,129	1,949	1,439	1,325
New York State	21.1	20.6	20.9	21.2	2,450	2,361	1,610	1,612
New York City	21.0	20.5	20.7	20.7	1,277	1,235	840	835
Maryland, resident	16.7	19.1	17.3	20.0	313	351	216	245
Baltimore, resident	21.0	24.3	23.3	24.6	151	174	111	118
Boston	25.4	25.0	30.0	28.6	154	150	121	114
Philadelphia	30.0	27.0	30.0	29.2	475	426	315	307
Toronto	17.6	15.2	19.3	14.5	88	76	64	48
Montreal, resident	18.4	17.3	18.6	17.0	145	134	98	88
London (Administrative County)	8.1	8.8	9.2	9.4	203	221	154	158
	Jan.-June		Jan.-Mar.		Jan.-June		Jan.Mar.	
England and Wales								
Total	8.4	8.1	9.7	8.9	1,829	1,777	1,062	961
Males	5.8	5.6	6.8	6.3	612	589	356	327
Females	10.7	10.5	12.4	11.3	1,217	1,188	706	634

Rates for the states and cities are based upon local estimates of population. United States data are based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in Current Mortality Analysis, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geograhic division; United States reporting area for the 10 per cent sample; first six and first nine months of 1951, 1952 and 1953

Geographic Division	Death Rates per 100,000*			Number of Deaths*		
	January—September					
	1953	1952	1951	1953	1952	1951
U. S. reporting area	16.0	16.2	16.4	1,896	1,877	1,881
New England	17.2	20.0	25.4	124	142	170
Middle Atlantic	22.4	22.0	18.1	526	510	415
East North Central	20.2	19.5	20.8	481	458	480
West North Central	16.8	17.7	18.2	183	192	195
South Atlantic	12.8	11.8	13.0	214	193	209
East South Central	8.6	9.9	10.6	74	87	93
West South Central	11.2	9.9	13.1	129	111	145
Mountain	11.4	15.5	10.1	47	61	39
Pacific	10.0	11.2	12.3	118	123	135
	January—June					
	1953	1952	1951	1953	1952	1951
U. S. reporting area	17.0	16.6	17.0	1,332	1,276	1,288
New England	18.3	20.9	26.4	87	98	119
Middle Atlantic	22.9	23.1	18.3	356	356	278
East North Central	21.1	20.8	22.2	333	324	339
West North Central	18.2	17.5	20.3	131	126	144
South Atlantic	14.1	11.7	13.1	156	127	140
East South Central	8.9	10.7	9.9	51	63	57
West South Central	13.6	9.3	12.2	103	69	89
Mountain	12.1	14.6	11.7	33	38	30
Pacific	10.4	10.4	12.6	82	75	92

*Excludes armed forces overseas.
These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."
Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3

Death rates per 100,000 from diabetes in the United States by geographic region and state, 1949-1950

Region and State	1950	1949	Region and State	1950	1949
United States	16.2	16.9			
New England	21.0	21.8	South Atlantic (con't)		
Maine	16.9	19.1	West Virginia	12.2	15.5
New Hampshire	20.1	23.3	North Carolina	9.8	10.2
Vermont	15.9	22.3	South Carolina	13.4	12.4
Massachusetts	20.5	20.2	Georgia	12.0	11.0
Rhode Island	35.9	38.7	Florida	12.7	13.3
Connecticut	19.3	19.3			
			East South Central	10.2	10.8
Middle Atlantic	20.5	20.1	Kentucky	11.9	12.2
New York	19.0	19.8	Tennessee	9.5	9.0
New Jersey	19.7	20.9	Alabama	8.9	11.0
Pennsylvania	23.0	20.2	Mississippi	10.8	11.3
East North Central	20.6	23.3	West South Central	11.6	11.6
Ohio	22.5	22.5	Arkansas	9.4	10.6
Indiana	17.9	18.2	Louisiana	12.5	13.3
Illinois	19.5	26.4	Oklahoma	13.4	14.2
Michigan	21.9	25.7	Texas	11.3	10.6
Wisconsin	19.5	18.9			
			Mountain	10.3	11.5
West North Central	17.9	17.7	Montana	11.5	18.1
Minnesota	17.0	17.0	Idaho	14.1	11.7
Iowa	17.4	16.3	Wyoming	11.4	11.2
Missouri	18.5	17.7	Colorado	10.9	12.7
North Dakota	17.6	18.4	New Mexico	5.6	6.8
South Dakota	17.8	20.6	Arizona	8.4	8.8
Nebraska	19.5	18.2	Utah	11.3	10.3
Kansas	17.9	19.1	Nevada	10.6	14.5
South Atlantic	12.6	13.0	Pacific	10.0	10.2
Delaware	27.0	26.0	Washington	14.2	14.3
Maryland	17.0	18.3	Oregon	11.2	12.5
Dist. of Columbia	15.1	14.2	California	8.8	8.9
Virginia	11.0	11.8			

Based on Sixth Revision of the International List. Excludes Armed Forces overseas.
Source: National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 4

Hospital discharges with a primary diagnosis of diabetes mellitus, number and average annual rate per 1,000 beneficiaries, 1950-1952, Saskatchewan Hospital Services Plan

Age	Annual Rate per 1,000 Beneficiaries			Aggregate Number of Discharges		
	Both Sexes	Males	Females	Both Sexes	Males	Females
All Ages	2.38	1.75	3.06	5,545	2,116	3,429
Under 1	—	—	—	—	—	—
1-4	.25	.28	.22	55	31	24
5-14	.57	.53	.61	244	116	128
15-24	.82	.64	1.00	298	114	184
25-44	1.06	1.11	1.00	678	358	320
45-64	4.77	2.90	7.07	2,032	678	1,354
65-69	11.66	7.21	18.17	952	349	603
70 & over	11.40	7.33	16.76	1,286	470	816

Source: Statistics from personal communication with Dr. Murray S. Acker, Assistant to the Deputy Minister, Department of Public Health, Province of Saskatchewan.

Rhode Island maintained its record of having the highest death rate from diabetes in the United States. Second rank continued to be held by Delaware. In general, the rates continued to be above the average in the industrialized areas of the North and East, and to be well below average in the South and Far West.

There is relatively little information on the rate of hospitalization for diabetes. It is difficult to assemble such information because there are no systematic collections of data on a wide scale on hospital admissions for a group of hospitals serving a specific population group of which the size and composition is known. In addition, it is not feasible to obtain causes of hospital admission as of the time of admission. A distinct contribution to this field are the data of the Saskatchewan Hospital Services Plan, which now covers more than

TABLE 5
Number and rate per 1,000 population of insulin-treated diabetics in Germany by province

Province or State	Number	Rate per 1,000 Population	Province or State	Number	Rate per 1,000 Population
Total Germany	58,921	.89	Hamburg*	2,500	1.67
Saxony-Anhalt	2,294	.55	Bremen	451	.82
Thuringia	1,665	.57	North Rhine Westphalia*	10,000	.85
Saxony*	10,000	1.78	Rhineland-Palatinate**	2,500	.90
Brandenburg	1,357	.54	Hesse	4,146	.96
Mecklenburg	1,905	.89	Wurttemberg-Baden*	3,000	.82
Berlin-East	2,114	1.80	Wurttemberg-Hohenzollern	689	.62
Berlin-West	3,262	1.54	South Baden	660	.55
Lower Saxony	6,202	.89	Bavaria	3,476	.38
Schleswig-Holstein*	2,700	1.0			

*Approximate figures
**Estimated
Source: Georg von Knorre, Die gegenwartige Diabetesmorbidität in Deutschland unter besonderer Berucksichtigung Sachsen-Anhalts. Ztschr. ges. Inn. Med., Jahrg. 6, 23-24: 725, 1951.

90 per cent of the population of the Province.* Figures on the annual rate of hospital discharges in which the primary diagnosis was diabetes mellitus are given in Table 4. The average annual rates per 1,000 beneficiaries during the period 1950 to 1952 are shown by sex and age. The figures give only a general picture of the situation because some patients are admitted more than once and because cases in which diabetes is a contributory cause of admission would not be included in the total diabetic discharges. Nevertheless, certain features of this experience are informative. For beneficiaries of both sexes the annual rate of discharge with primary diagnosis of diabetes was 2.38 per 1,000. The rate for females was 75 per cent greater than that of males. The rate increased steadily with age, accelerating between ages 45 and 70. After age 70, the rate showed little change. The differences in the rate between the sexes were most marked after age 45, when the female rate was consistently more than double that for males.

The method of insulin distribution in Germany makes it possible to ascertain the number of diabetics using insulin in the various civil divisions of the country. The data which have been assembled and published in an article by von Knorre are shown in Table 5. The dates of observation for the individual areas were between 1948 and 1950, about half of them in the latest year. The number of insulin-treated diabetics per 1,000 population shows a considerable range, from a low of .38 in Bavaria to a high of 1.80 in Eastern Berlin. These figures, however, can be accepted only to a very limited degree as indicative of the regional variations in the prevalence of diabetes. They reflect differences also in the composition of the population, in clinical usage of insulin, perhaps also in its availability and cost as well as in the completeness of reporting.

Certainly the proportion of diabetics using insulin differs widely from place to place. This is brought out in other data in von Knorre's article which give facts on the total diabetics and insulin-using diabetics in smaller civil divisions of Saxony-Anhalt. It is interesting to compare this author's data on the two sectors of Berlin with the more recent figures on the total diabetic population reported by Schliack*. The latter gives the total number of diabetics in the Eastern sector of Berlin as 4,094 and 11,294 in the Western sector of the city, as against 2,114 and 3,262 insulin-using patients respectively reported by von Knorre. It is doubtful that the proportion of patients on insulin treatment differs in the two sectors as much as the figures from the two sources would indicate.

*For fuller details on the program and facts on its utilization, see the article, "Health Services for the Aging in Saskatchewan," by L. S. Rosenfeld, F. D. Mott, and M. G. Taylor, Illness and Health Services in an Aging Population, Public Health Service Publication No. 170, Federal Security Agency, Washington, 1952.

*Volker Schliack, Die Diabetespopulation Berlins, Manifestations-und Lebensalter. Ztschr. Klin. Med., 150:326, 1953.

ABSTRACTS

Banerjee, Sachchidananda; Belavady, Bhavani; and Mukherjee, Achintya Kumar *(Dept. of Phys., Presidency College, Calcutta, India)*: EFFECT OF DEHYDROASCORBIC-ACID IN RABBITS. Proc. Soc. Exper. Biol. & Med., *83*:133, May 1953.

Intravenous injections of dehydroascorbic acid in rabbits in a dose of 1.0 to 1.5 gm. per kg. could not produce either persistent hyperglycemia or persistent diabetic type of glucose tolerance curve. An immediate transitory rise in blood sugar could be prevented by a prior injection of the adrenergic blocking drug, dihydroergotamine methanesulfonate. Rabbits injected with dehydroascorbic acid neither excreted sugar in the urine nor showed any histologic changes in the pancreas, suprarenal and pituitary. The authors conclude that dehydroascorbic acid is not diabetogenic in rabbits, although other workers (Patterson) have reported that it is in rats.

Beidleman, Barkley; Principato, Luigi A.; and Duncan, Garfield G. *(Med. Cen. Clin., Pensacola, Fla.; Pennsylvania Hosp., Philadelphia, Pa.; Pennsylvania Hosp. and Benjamin Franklin Clin., Philadelphia, Pa.):* COMPARATIVE EFFECTS OF INSULIN ADMINISTERED INTRAVENOUSLY AND SUBCUTANEOUSLY. Metabolism 2:211-17, May 1953.

In 10 nondiabetic and 10 diabetic patients under the conditions of the tests as described, regular insulin administered intravenously acted more rapidly and produced lower blood sugar levels than regular insulin given subcutaneously. In these two groups of patients, subcutaneous insulin allowed an initial hyperglycemia not evident with intravenous insulin. In nondiabetics, the average duration of effect of insulin given intravenously was three hours as against almost eight hours for insulin given subcutaneously. However, in the diabetic patients tested, the average duration of effect of insulin by both routes was three hours. The therapeutic aphorisms underlying the recommendations for the use of insulin intravenously in diabetic coma and in circulatory shock are supported by these findings.

Bergman, Per *(Kvinnokliniken, Allmänna sjukhuset, Malmö, Sweden):* DIABETES IN PREGNANCY. REPORT OF A SERIES AND CONSIDERATIONS OF PRINCIPLES OF TREATMENT. Nord. Med. *49*:168, January 30, 1953.

An account is given of 72 pregnancies in 45 diabetics seen at the Gynecological Department of Malmö General Hospital during the last 40 years (1912-1951). No difference was found between the fetal prognosis of pregnancies occurring 2 years or less before detection of the disease and those occurring afterwards. The fetal prognosis of pregnancies antedating the discovery of diabetes by more than 2 years was not found to be influenced by the disease. Evidence of toxemia was noted in 39 per cent of the pregnancies. In this series toxemia of pregnancy had no apparent influence on the fetal prognosis (26 pregnancies with associated symptoms of toxemia ended in 17 live births). The duration of the disease before pregnancy had no appreciable effect on the prognosis of the fetus. Hormonal therapy (estrogen and progesterone) was tried in some of the women, but it did not seem to produce effects superior to those obtained without the use of hormones. Intrauterine death occurred in 10 of 33 cases in which pregnancy had proceeded to the 36th week or more and in which cesarean section was not done. There is reason to believe that some of these intrauterine deaths could have been prevented by cesarean section in the 36th to 37th week of pregnancy.

Bo, Walter J.; and Atkinson, William B. *(Dept. of Anat., Univ. of Cincinnati Coll. of Med., Cincinnati, Ohio):* HISTOCHEMICAL STUDIES ON GLYCOGEN DEPOSITION IN UTERUS OF THE RAT. III. EFFECT OF STARVATION. Proc. Soc. Exper. Biol. & Med. *83*:405-07, June 1953.

Relatively short periods of fasting result in the rapid disappearance of glycogen from the liver and skeletal muscle of hypophysectomized animals. In spite of the depletion of carbohydrate reserves in the starved hypophysectomized castrate rat, estrogen promotes the deposition of glycogen in the uterine musculature in amounts

comparable to those deposited in well-nourished animals. In this respect this action of estrogen on the uterus is analogous to that of certain of the hormones of the anterior hypophysis and adrenal cortex on the deposition of glycogen in the liver and skeletal muscle.

Brown, J. H. U. *(Sch. of Med., Univ. of North Carolina, Chapel Hill)*: THE INFLUENCE OF DDD ON THE COURSE OF ALLOXAN DIABETES IN THE ADULT RAT. Endocrinology 53:116-18, July 1953.

Nichols and Gardner (1951) demonstrated that animals fed DDD (2,2 bis-(parachlorophenyl)-1,1-dichloroethane) developed adrenal cortical atrophy and became insulin sensitive. In this study, animals fed DDD after alloxan treatment lose signs of diabetes, including high blood sugar.

Bucht, Härje; Werkö, Lars; and Ek, Jan. *(S:t Eriks sjukhus, Stockholm, Sweden)*: RENAL FUNCTION STUDIES IN DIABETIC NEPHROPATHY. Nord. Med. 49:470, May 27, 1953.

Renal clearances for PAH, inulin, and creatinine were determined in 21 cases of diabetes mellitus, with varying degrees of renal damage. In 9 cases the extraction of PAH was determined after renal venous catheterization. In these cases the tubular absorptive capacity for glucose was also determined. The extraction of PAH was close to normal when the inulin clearance was above 40-50 ml. per min. but markedly lower in the cases with lower inulin clearance. The decrease of PAH and glucose-Tm respectively, with increasing renal damage, paralleled each other and also the lowering of inulin clearance. The changes found in these cases were essentially similar to these found in cases with chronic nephritis.

Cochrane, Gilbert C.; Michaels, George D.; and Kinsell, Laurance W. *(Inst. for Metabolic Res. of the Highland Alameda County Hosp., Oakland, Calif.)*: DIETARY MODIFICATIONS OF PLASMA CHOLESTEROL AND PHOSPHOLIPID LEVELS IN DIABETIC PATIENTS: THE EFFECTS OF MIXED DIETS HIGH IN VEGETABLE FAT. J. Clin. Nutrition 1:295-98, May-June 1953.

Substitution of vegetable fat for "animal fat" in high-protein, high-fat, diabetic diets (the total protein, fat, and carbohydrate content remaining unchanged) resulted in a major fall in levels of plasma cholesterol and phospholipids in diabetic patients and in one patient with "familial hypercholesterolemia." In one patient with severe diabetes, the *addition* of 134 gm. of vegetable fat (as nuts) to a high-animal-fat "standard" diabetic diet also resulted in a slow but major fall in plasma lipids.

Cohen, Aharon M.; and Rachmilewitz, M. *(Med. Dept. and Clin. Res. Lab., Hadassah Univ. Hosp., Hebrew-Univ.-Hadassah Med. Sch., Jerusalem, Israel)*: EFFECT OF AUREOMYCIN IN RATS WITH CHRONIC ALLOXAN DIABETES. Proc. Soc. Exper. Biol. & Med. 83:50-52, May 1953.

Aureomycin given to chronic alloxan-diabetic rats in daily doses of 20 mg. per 100 gm. of food caused an average gain in body weight of 19.0 ± 2.9 gm. during 28 days. Control chronic alloxan-diabetic rats gained 9.6 ± 2.0 gm. during the same period. During aureomycin administration, the animals consumed more food and had increased glycosuria and diuresis.

Coll, Pablo Liendo *(Instituto Nacional de Nutrición)*: DIET AND DIABETES. PRACTICAL CONSIDERATIONS. Archivos Venezolanos de Nutrición 3:37-44, June 1952.

This paper deals with the problems of feeding patients from the point of view of the hospital dietetic department. In it theoretical considerations have been avoided as much as possible. Rules for calculating amounts of nutrients, choice of food, and distribution of meals are given.

Conard, V.; Franckson, J. R. M.; Bastenie, P. A.; Kestens, J.; and Kovacs, L. *(Clin. Méd de L'Hôp. Brugmann, Univ. Bruxelles, Ed Reine Elisabeth Fond.)*: CRITICAL STUDY OF THE TRIANGLE OF INTRAVENOUS HYPERGLYCEMIA IN NORMAL MAN AND THE DETERMINATION OF A GLUCIDE ASSIMILATION COEFFICIENT. Arch. Internat. de Pharmacodyn. 93:277-92, 1953.

In twenty normal persons, an intravenous test for hyperglycemia and measurement of the volume of extracellular fluid were carried out simultaneously. By this means, it is possible to differentiate between the diffusion of glucose and its cellular penetration and to as-

certain that the descending slope of the intravenous hyperglycemic curve is a unique function of assimilation.

Coulson, Roland A.; and Hernandez, Thomas *(Dept. of Biochem., Louisiana State Univ. Sch. of Med., New Orleans, La.):* GLUCOSE STUDIES IN CROCODILIA. Endocrinology *53*:311-20, September 1953.

Injected glucose is removed from the blood stream of the alligator at a very slow rate. This rate is determined by the temperature of the animal and is a function of the metabolic rate. One unit of "insulin" per gm. body weight produces an immediate state of "shock," which lasts a few hours. This condition occurs during the period of hyperglycemia. A second state of "shock," which is due to hypoglycemia, follows more than a day later. Adrenalin reduces the glycogen stores of the liver to about 1/3 the normal value and the body glycogen to about ½ the normal in 24 hours.

Dlugach, Joseph *(Philadelphia, Pa.)*: DIABETES MELLITUS IN A CAT. J. Am. Vet. M.A. *123*:118-19, August 1953.

A case report. In the hospital a close watch was kept on the cat's stools for signs of pancreatitis, but none were observed.

Drew, A. L.; and Selving, B. T. *(Univ. of Michigan, Ann Arbor)*: OBSERVATIONS ON PENTOSURIA IN NEUROMUSCULAR DISORDERS. Neurology *3*:563-68, August 1953.

First morning specimens were obtained from 31 cases of muscular dystrophy, myotonia dystrophica, and myotonia congenita (all positive for pentosuria) and muscular atrophy (negative for pentosuria) after 24 to 48 hours on fruit-free diets. Testing was done with osazone preparation with phenylhydrazine after removal of fermentable sugars, creatinine, creatine and uric acid with Lloyd's reagent and finally glycuronates and polyphenols with mercuric nitrate.

Dury, Abraham; and Treadwell, Carleton R. *(Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Pa.):* HORMONAL INFLUENCES ON LIVER LIPID PARTITION, CARBOHYDRATE AND ELECTROLYTE METABOLISM IN THE RAT. Proc. Soc. Exper. Biol. & Med. *82*:719-27, April 1953.

The effects of insulin, epinephrine, and intravenous glucose administration on the liver lipid partition, water, sodium and potassium content of liver and plasma, liver glycogen, and plasma glucose in intact, adrenalectomized, and adrenalectomized-alloxan rats were studied. In the adrenalectomized rat, carbohydrate oxidation and lipogenesis or neutral fat mobilization were greater than in the intact rat. Comparison with the adrenalectomized-alloxanized group suggested that glucose oxidation in the adrenalectomized group was proceeding under the unopposed action of insulin, since in the former group the metabolic status was ameliorated during the condition of dual-glandular insufficiencies (adrenal and insulin). Lipid changes were ascribed mainly to the absence of the hormonal influences of the adrenal gland. However, significant changes in the fractions of liver lipids followed the injection of insulin and epinephrine. In the absence of insulin and adrenal gland secretions, there was a decrease in the level of fat metabolism following the glucose infusion.

Changes in the level of liver lipids occurred with much greater rapidity (30 to 60 minutes) than is generally recognized. The changes in the levels of phospholipids and neutral fat were always in opposite direction while changes in the cholesterol fractions paralleled those for the phospholipids. Shifts in the lipid pattern occurred frequently, without significant changes in the total fat content of the liver.

Editorial *(New York)*: DIETARY FACTORS IN THE ETIOLOGY OF DIABETES MELLITUS. Nutrition Rev. *11*:269-70, September 1953.

The incidence of diabetes generally was found to be highest where medical care and general economic welfare were highest. Himsworth and also Suvarakich have concluded that it is most prevalent where high-fat diets are consumed. The low incidence in Thailand was attributed to the national diet based on rice, in which fat accounts for only 10 per cent and protein for 9 per cent of the nutrients. However, observations in Iceland by Albertsson do not support this. Here the incidence on careful study was less than 1 per 1,000, and the annual diabetic death rate 1.9 to 4.0 per 100,000 compared with 26.9 for the United States. Short life expectancy does not account for this difference. Present

Icelandic diet contains about 44 per cent carbohydrate, 45 to 58 per cent protein composed almost entirely of milk, meat, and fish, and the remainder fat. Albertsson believes the lack of obesity in Thailand and Iceland more significant than dietary composition.

Foreign Letters—Pihl, A. (*Nutrition Res. Inst., Univ. of Oslo, Norway*): CHOLESTEROL STUDIES. J.A.M.A. *152*:73, May 2, 1953.

Pihl has contributed to the Scandinavian Journal of Clinical and Laboratory Investigation studies on the cholesterol content of foods and on the relationship of cholesterol to atherosclerosis. He concludes that the endogenous regulation of cholesterol metabolism and the level of fat and caloric intake may be a more important factor in vascular diseases than the level of cholesterol consumption.

Fox, James Rogers (*Student Health Serv., Univ. of Minnesota, Minneapolis*): THE INCIDENCE OF DIABETES MELLITUS AND GLYCOSURIA IN 19,358 COLLEGE STUDENTS. Journal-Lancet *72*:479-81, 500, October 1952.

Of the 19,358 patients examined, 155, or about 80 cases per 10,000, had glycosuria. This incidence is identical with that found by Blotner. At the same time, 70 or 36 per 10,000 population cases of diabetes were found, but this figure comprised 45 per cent of the total persons with glycosuria in contrast to the 57 per cent reported by Blotner. In addition, the patients with renal glycosuria totaled 32, or 16 cases per 10,000. There were 47 cases of glycosuria with a normal curve and no renal evidence, which were classed as normal variance. These were 24 per 10,000. In addition, there were 6 cases of what has been termed "temporary hyperglycemic glycosuria" in which the fasting blood sugar was normal, the blood sugar peak was high, but the return to normal of the curve was definite in an hour and a half.

Friedman, Meyer; Byers, Sanford O.; and Gunning, Barbara (*Harold Brunn Inst., Mount Zion Hosp., San Francisco, Calif.*): OBSERVATIONS CONCERNING PRODUCTION AND EXCRETION OF CHOLESTEROL IN MAMMALS. Am. J. Physiol. *172*:309-16, February 1953.

The intravenous injection of a moderate amount of cholesterol in the form of hypercholesteremic serum into the rat leads to a hypercholesteremia which disappears in 12 to 24 hours. The liver was found to be chiefly responsible for the removal of excess cholesterol from blood. Evidence was presented which suggested that at least 60 per cent of the cholesterol injected was converted and excreted as bile acid.

Gauchat, Robert D. (*Dept. of Pediat., State Univ. of Iowa Hospitals, Iowa City, Iowa*): PROBLEMS POSED BY THE NEWBORN INFANT OF A DIABETIC MOTHER. J. Iowa M. Soc. *43*:416-24, October 1953.

The newborn infant from a prediabetic or diabetic mother has developed in an environment characterized by excessive stimulation by both anterior pituitary and adrenocortical hormones, secondary to hormonal alterations in the diabetic mother. The characteristic habitus of the infant reflects the influence of these hormonal stimuli. Following birth, the infant is in a period of relative hypopituitarism and hypoadrenocorticism, the effects of which become clinically obvious about 2 to 4 hours postpartum and may lead to death in 18 to 36 hours.

Gitlin, David (*Dept. of Pediat., Harvard Med. Sch, and Children's Med. Cent., Boston, Mass.*): THE IMMUNOCHEMICAL HETEROGENEITY OF HUMAN PLASMA β-LIPOPROTEIN. Science *117*:591-93, May 29, 1953.

The plasma β-lipoprotein fraction of normal human plasma is composed of a number of lipoproteins differing markedly in their immunochemical characteristics and present in varying ratios in the individual plasmas.

Since the level of individual lipoproteins is a reflection of tissue metabolism, the possible relationships between tissue metabolism and hyperlipoproteinemia in disease await further study, especially the suggestion that a definite distribution of physical heterogeneity of circulating lipoproteins as demonstrated by the ultracentrifuge is intimately associated with certain pathological states such as atherosclerosis.

Hamilton, Gwyneth M. (*The Birmingham and Midland Hosps. for Women*): OVARIAN CYSTS IN THE NEWBORN INFANT OF DIABETIC MOTHER. J. Obst. & Gynaec. Brit. Emp. *60*:533-34, August 1953.

Two cases of follicular ovarian cysts occurring in new-

born infants of diabetic mothers are described. It is suggested, in confirmation of other work, that they are the result of the excessive production of pituitary gonadotrophins. Increased stimulation of the anterior pituitary as a whole in maternal diabetes is shown by the production of a large fetus with hyperplasia of the islands of Langerhans of the pancreas and the formation of follicular ovarian cysts.

Hampton, H. Phillip (*Tampa, Fla.*): THE USE OF INSULIN IN DIABETES. J. Florida M. A. *40*:170-72, September 1953.

In order to encourage more diabetic patients to follow principles which will control their abnormal carbohydrate metabolism, it is important not to overcomplicate the methods of control. Contrarily, oversimplification will lead to laxity of control and increased complications. The use of insulin provides a means by which diabetic patients may be guided to a healthy, full life by intelligent medical management.

Herzstein, Joseph; Chun-l, Wang; and Adlersberg, David (*Mt. Sinai Hosp., New York, N.Y.*): FAT-LOADING STUDIES IN RELATION TO AGE. A. M. A. Arch. Int. Med. *92*:265-72, August 1953.

A fat-loading test consisting of a cream, tea, sugar, and bread meal representing 1 gm. of fat per kilo of body weight was given to 10 subjects with a mean age of 24.9 years and 11 subjects with a mean age of 62 years, all nondiabetics. Total serum lipids were determined at 0, 2, 4, 6, 12, and 24-hour intervals. (The chylomicron count previously used in such studies by others was not found adequate by these authors.) No significant difference in the pattern of the rise and fall in lipemia was noted in the two groups, although the maximum rise occurred later in the older group.

Hesselbach, M. L.; and duBuy, H. G. (*Fed. Security Agcy., Pub. Health Serv., Nat. Insts. of Health, Nat. Microbiological Inst., Bethesda, Md.*): LOCALIZATION OF GLYCOLYTIC AND RESPIRATORY ENZYME SYSTEMS ON ISOLATED MOUSE BRAIN MITOCHONDRIA. Proc. Soc. Exper. Biol. & Med. *83*:62-65, May 1953.

Washed mouse brain mitochondria carried out the complete enzymic conversion of exogenous glucose to carbon dioxide and water. Glycolysis took place anaerobically and aerobically, with the production of lactic acid. Under aerobic conditions, glucose was oxidized by means of a malonate-sensitive cycle. The accumulation of lactic acid was correspondingly decreased. In contrast, the supernatant carried out anaerobic and aerobic glucolysis, but not respiration of glucose. The submicroscopic particle fraction did not carry out the reactions of either system.

Houssay, B. A.; Rodriguez, R. R.; and Cardeza, A. F. (*Instituto de Biologia y Medicina Experimental—Costa Rica 4185—Bs. As.*): THE DIABETOGENIC ACTION OF THE GROWTH HORMONE OF THE HYPOPHYSIS. Rev. Soc. argent. biol. *29*:33-41, April-May 1953.

After a large pancreatectomy (resection of 77 and 87 per cent of the pancreatic mass), dogs became very sensitive to the diabetogenic action of two growth hormone preparations. The preparation obtained by the Raben method also showed a definite diabetogenic action. The Armour preparation of growth hormone obtained by the Wilhelmi-Fishman-Rusell method had more growth-promoting and more diabetogenic activity than the Armour preparation of growth hormone obtained by the Raben method. The diabetogenic action of the growth hormone preparation was observed in the absence of the thyroid. Both types of growth hormone preparations may produce permanent diabetes, with hydropic degeneration (glycogen infiltration) of the beta cells of the islets of Langerhans.

Ingle, Dwight J.; Beary, Dexter F.; and Purmalis, Andrejo: (*Upjohn Laboratories, Kalamazoo, Mich.*): COMPARISON OF THE EFFECT OF 11-KETOPROGESTERONE, 11*a*-HYDROXYPROGESTERONE AND 11β-HYDROXYPROGESTERONE UPON THE GLYCOSURIA OF THE PARTIALLY DEPANCREATIZED RAT. Endocrinology *53*:221-25, August 1953.

After the establishment of the presence of diabetes in the rats (male), force feeding was carried out twice daily and urinary glucose determined on 24-hour specimens before, during and after the test injections. After 11*a*-hydroxyprogesterone, up to 50 mg. daily, there was only a small increase in glycosuria. After 11-ketoprogesterone, up to 16 mg. daily, glycosuria increased to 2½ times that of control. After 11β-hydroxyprogesterone, glycosuria

became 2¾ times that of control. Finally, in one adrenalectomized diabetic rat, glycosuria was increased 7 times the control period.

Jasper, D. E. *(Sch. of Veterinary Med., Univ. of California, Davis, Calif.):* ACUTE AND PROLONGED INSULIN HYPOGLYCEMIA IN COWS. Am. J. Vet. Res. *14*:184-91, April 1953.

Two units of insulin per kilogram intravenously gave a maximum effect in reducing blood glucose, whereas one unit did not. Increasing insulin dosage up to 10 units per kilogram increased duration but not depth of hypoglycemia. The rate of fall of blood glucose after insulin injection was relatively constant, appearing to be between 25 and 40 mg. per 100 cc. of blood in thirty minutes. The rate was independent of insulin dosage. Mild hypoglycemic symptoms were observed in 1 of 2 cows receiving single injections of 2, 5, and 10 units of insulin per kilogram. Prolonged insulin hypoglycemia will result in a convulsive, hypoglycemic crisis, which responds well to glucose injections. Cows are able to withstand short periods of extreme hypoglycemia much more readily than a prolonged period at a significantly higher blood glucose level.

Jasper, D. E. *(Sch. of Veterinary Med., Univ. of California, Davis, Calif.):* PROLONGED INSULIN HYPOGLYCEMIA IN SHEEP. Am. J. Vet. Res. *14*:209-13, April 1953.

Eight ewes were subjected to prolonged insulin hypoglycemia, and the symptoms were recorded. Symptoms were classified according to severity into three stages. Severity of symptoms was dependent not only upon depth of hypoglycemia but to a large degree upon duration as well. Little or no difference in glycemic levels was apparent between the different stages of symptoms observed, duration of hypoglycemia being the determining factor. Marked symptoms often persist for several hours or days following spontaneous or induced return to normal or hyperglycemic levels. In the ewe, it is difficult to produce a hypoglycemia below 5 mg. per 100 cc. of blood.

Johnson, Doris *(Director of Dietetics, Grace-New Haven Community Hosp. and Ass. Prof. of Public Health, Yale Sch. of Med., New Haven, Connecticut):* DIETOTHERAPY. J. Clin. Nutrition *1*:309-14, May-June 1953.

The value of the use of the "exchange" system is presented.

Joos, Thaddeus H. *(U.S. Navy Med. Corps):* LATE COMPLICATIONS IN JUVENILE DIABETES. Henry Ford Hosp. M. Bull. *1*:18-20, September 1953.

In the regulation of diabetes mellitus in children, control is of the utmost importance. There is a steady accumulation of information showing that good control will lead to a lowered incidence of complications, especially retinopathy, hypertension, and albuminuria. To obtain this control, a diet allowing a moderate amount of carbohydrate can be used with success. Such a diet has been used in the cases reported with 15 per cent of total calories from protein, 50 per cent from fat, and 35 per cent from carbohydrate.

Joslin, Elliott P. *(Boston, Mass.):* DIABETIC COMA. Pennsylvania M. J. 56:355-59, May 1953.

Diabetic coma is the end result of the uncontrolled diabetic, and the more diligently we try to control diabetes the less coma deaths we have. Diabetes should be as safe in the home as in the hospital. This is possible only if the diabetic and his family receive education—primary, secondary, and postgraduate. Even though we send them to diabetes camps, the instruction is inadequate, although from one another they learn almost automatically how to adjust diet, insulin, and exercise. The trouble really begins later. They are led astray because they see that almost any diabetic with insulin will live 10 or 12 years, although the control is lacking. What they do not realize is that "The wages of sin is death." Never will they grasp that point until, by contact with the diabetics of 15 or 20 years' duration, they can see the plight of the neglected case for themselves.

KIRTLEY, W. R.; WAIFE, S. O., AND PECK, F. B. *(Lilly Res. Labs. and Indianapolis Genl. Hosp., Indianapolis, Ind.):* EFFECT OF GLUCAGON IN STABLE AND UNSTABLE DIABETIC PATIENTS. Proc. Soc. Exper. Biol. & Med. *83*:387-89, June 1953.

A highly purified preparation of glucagon (pancreatic

hyperglycemic-glycogenolytic factor, HGF) was administered intravenously to normal and diabetic subjects in doses of 10 μg per kg. of body weight (10 μg equals 20 "cat units"). The 8 diabetic subjects had two different types of response in blood sugar and serum inorganic phosphorus. In 4 "stable" diabetics the blood sugar showed a delayed fall and an impaired fall in phosphorus as compared with normals. In the other 4 diabetics, 3 of whom were of the "unstable and insulin-sensitive" type, the blood sugar did not rise as high, but the phosphorus fell in a manner similar to normals.

Larralde, E. Rivas *(Instituto Nacional de Nutrición):* DIETETIC TREATMENT OF DIABETES. Archivos Venezolanos de Nutrición 3:25-36, June 1952.

The author gives a brief historic summary of the evolution of knowledge of dietetics and its application to diabetics. The author favors an eclectic policy between the different proposed methods of free diet and the diet of the conservative school.

Lynch, Robert C. *(Tulane Univ. of Louisiana Sch. of Med.; and the Ochsner Clinic, New Orleans, La.)*: SURGICAL PROCEDURES IN PERIPHERAL ARTERIAL DISEASE. S. Clin. North America 33:953-65, August 1953.

A brief review of the surgical treatment of peripheral arterial disease is presented. The author strongly recommends sympathectomy in the treatment of obliterative vascular disease, especially when accompanied by diabetes.

Mackler, Bruce; and Guest, George M. *(Children's Hosp. Res. Foundation and the Dept. of Pediat., Univ. of Cincinnati, Cincinnati, Ohio):* EFFECTS OF INSULIN AND GLUCOSE ON UTILIZATION OF FRUCTOSE BY ISOLATED RAT DIAPHRAGM. Proc. Soc. Exper. Biol. & Med. 83:327-29, June 1953.

In isolated rat diaphragm, insulin increased the metabolism of fructose and glucose via the hexokinase system but did not affect the utilization of fructose via the fructokinase pathway. The results suggest that insulin affects the metabolism of glucose and fructose by accelerating their initial phosphorylation by hexokinase.

Mateer, F. M.; Garver, K. L.; Sakol, M. J.; and Danowski, T. S. *(Dept. of Res. Med. and Children's Hosp. of Pittsburgh., Univ.of Pittsburgh Sch. of Med., Pittsburgh, Pa.)*; HYALURONIDASE AND THE SUBCUTANEOUS ADMINISTRATION OF ELECTROLYTE-FREE GLUCOSE SOLUTION. Am. J. M. Sc. 226:139-42, August 1953.

The authors report that the administration to diabetic children of electrolyte-free 5 per cent glucose solution in volumes in ordinary clinical use induces similar biochemical and circulatory changes, regardless of whether or not hyaluronidase is added. The fact that subcutaneous administration of saline-free fluids results in pooling or segregration of extracellular electrolyte necessitates caution in such therapy in patients already depleted.

Mayer, J.; and Hagman, Norma C. *(Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.):* TOTAL BODY WATER AND BLOOD VOLUME IN HEREDITARY OBESE-HYPERGLYCEMIC SYNDROME OF MICE. Proc. Soc. Exper. Biol. & Med. 82:647-49, April 1953.

Total body water and blood volume were determined in mice with the hereditary obese hyperglycemic syndrome and in littermate controls. Only 12 per cent of the excess weight of obese animals was found to be represented by water. Blood volume was not increased in obese animals. The total body water and percentage of weight represented by water in young obese animals were similar to those in nonobese animals of the same weight.

McKay, Donald G.; Benirschke, Kurt; and Curtis, George W. *(Pathol. Dept. of Boston Lying-in Hosp., & Dept. of Pathol. Harvard Med. Sch., Boston, Mass.)*: INFANTS OF DIABETIC MOTHERS: HISTOLOGIC AND HISTOCHEMICAL OBSERVATIONS ON THE PANCREAS. Obst. & Gynec. 2: 133-38, August 1953.

Charcot-Leyden crystals have been observed in the eosinophilic inflammatory infiltrate around the islets of Langerhans in the pancreas of infants of diabetic mothers. From these observations it is suggested that maternal hyperglycemia, whether constant or intermittent, causes fetal hyperglycemia, which in turn results in increased insulin formation by the fetal pancreas and hypertrophy and hyperplasia of the fetal islets of Langerhans. Some unknown substance, possibly related to insulin, diffuses into the connective tissue around the islets. This material, which may be rich in sulfhydryl groups, attracts eosino-

phils and leads to the marked peri-islet inflammation. With breakdown of the eosinophils, Charcot-Leyden crystals appear in the areas of inflammation.

McQuown, Albert L. (*Baton Rouge, La.*): PATHOGENESIS OF DIABETES. New Orleans M. & S. J. *104*:652-53, October 1952.

The condition of diabetes mellitus is a complex hormonal interplay of carbohydrate metabolism and not a simple pancreatic change producing hypoinsulinism. This understanding is essential for the modern-day treatment of diabetes; and it is not too much to hope that as our knowledge of these basic hormone activities and interrelationships increase, the reason for the widespread incidence of diabetes in man will be revealed.

Mikhail, Maurice N. (*Dept. of Clin. Path., Farouk I Univ., Alexandria, Egypt*): A SIMPLE AND QUICK METHOD FOR BLOOD SUGAR ESTIMATION AT THE BEDSIDE. Journal of the Royal Egyptian Medical Association *35*:402-09, July 26, 1952.

A bedside method for the determination of blood sugar in 10 minutes, using only test tubes, is presented. The method depends on the reduction of copper and subsequent direct vision matching of the color, produced on adding phosphomolybdic acid solution, against permanent standards. The error is within the limits of +4 per cent and —6 per cent.

Mirsky, I. Arthur; and Perisutti, Gladys (*Pittsburgh, Pa.*): THE INACTIVATION OF INSULIN BY LIVER SLICES OF THE RAT. Endocrinology *52*:698-704, June 1953.

Like homogenates and extracts of liver, surviving liver slices inactivate insulin *in vitro*. This inactivation is dependent both upon the quantity of liver employed and the length of the incubation period. As with homogenates, the addition of insulinase-inhibitor to the incubation mixture results in a significant reduction in the insulinase activity of liver slices. With slices, however, the spontaneous rate of insulin inactivation is much slower than with homogenates of equivalent amounts of liver. Consequently, it may be concluded that within the intact cell only a portion of the potential insulinase is active, the remainder being inhibited by an insulinase-inhibitor. The insulinase activity of homogenates or extracts from fasted rats is markedly diminished. Slices of liver from similarly fasted rats, however, exhibit a definite tendency to destroy more insulin than do those from fed rats. Since the inactivation of insulin probably is dependent upon the balance between insulinase and insulinase-inhibitor, the discrepancy between the activity of homogenates and that of slices of livers from fasted rats may be attributed to a greater decrease in the inhibitor than in the insulinase.

The aforementioned postulates are in accord with established data concerning the phenomenon of "starvation diabetes." Thus, the fasted animal not only responds to the ingestion of carbohydrate with a typical "diabetic tolerance" curve but also shows a decreased hypoglycemic response to the injection of insulin. The relevance of insulinase and insulinase-inhibitor to the etiology of diabetes mellitus in man is difficult to evaluate at the present time. The presence of these factors in extracts of liver and the demonstration that they are effective in the intact cell lends support to the hypothesis that an insufficiency of insulin may result from an increased destruction of insulin either in consequence of an increase in insulinase activity or of a decrease in the availability of the insulinase-inhibitor.

Mosenthal, Herman O. (*New York, N. Y.*): INSULIN AND DIABETES ENDOGENOUS AND EXOGENOUS INSULIN. Rev. Gastroenterol. *20*:373-85, June 1953.

The author believes that a high level of blood sugar without glycosuria has no detrimental influence upon diabetes. On the other hand, marked glycosuria, polyuria, dehydration, lack of deposit of liver glycogen and protein destruction will have harmful effects upon the diabetic; it is in these changes that the cause for retinitis, nephritis, arteriosclerosis and coronary thrombosis, the frequent complications of diabetes, must be sought.

He postulates a difference in effect between the insulin secreted by the pancreas, endogenous insulin and injected exogenous insulin. Insulin secreted by the pancreas passes to the liver where a large part is retained for action upon the glucose carried by the portal vein from the intestinal canal to the liver. Insulin is in large part bound and retained in reserve by the tissue which it first contacts. Hence, endogenous insulin exerts its main influence through the liver, while exogenous insulin affects principally the extrahepatic tissues. A great

leeway exists in the amount of insulin the body can take care of without changing the blood sugar from a normal level. The amount of insulin usually secreted by the pancreas, the basic insulin, is probably greater than the body needs; some of this may be stored in the liver for the full control of meals to come, and some of it may be taken up by the peripheral tissues to enable them to utilize glucose. When the basic insulin secretion is curtailed to the extent that the fasting blood sugar becomes elevated, the use of insulin becomes obligatory.

Munro, H. N.; and Thomson, W. S. T. (*Dept. of Biochemistry, The Univ. of Glasgow, Scotland*): INFLUENCE OF GLUCOSE ON AMINO ACID METABOLISM. Metabolism 2:354-61, July 1953.

In the plasma, total amino nitrogen estimations and microbiological assays of tryptophan, histidine, leucine, isoleucine, threonine, arginine and valine have been used to study the protein-sparing effect of glucose and fat on six human subjects. Glucose ingestion caused a 12 per cent reduction in the amino nitrogen which was maximal at one hour, whereas fat ingestion resulted in a much more gradual fall, to the extent of 4 per cent of the initial value; the effect of fat was of doubtful statistical significance. Similar experiments on rats confirmed the differences in action of carbohydrate and fat. The level of the individual amino acids fell after glucose ingestion to varying extents. If these depressions were arranged in the form of a ratio, with tryptophan as unity, and compared with Rose's estimates of the human requirements for these amino acids arranged in a similar way, then there was observed to be a close similarity between the values. This suggests that glucose stimulates protein synthesis. These findings have been discussed in relation to the action of glucose on dietary protein taken in the same meal.

Murray, Hazel C.; and Rosenberg, M. M. (*Dept. of Foods and Nutrition and Poultry Husbandry, Univ. of Hawaii, Honolulu, Hawaii*): STUDIES ON BLOOD SUGAR AND GLYCOGEN LEVELS IN CHICKENS. Poultry Sc. 32:805-11, September 1953.

The normal sugar concentration of venous blood from mature New Hampshire pullets was found to be 182.5 mg. per cent. When they were fasted, the blood sugar levels dropped and, after 3 hours, stabilized at a significantly lower plateau. When pullets starved 16 hours were returned to a practical type layer ration, the blood sugar level returned to normal within 1 hour. No detectable glycogen remained in the livers of six-week-old New Hampshire cockerels following 16 hours of fast. The liver glycogen concentration increased hourly to 7 hours on feed. At that time the average glycogen content of 12 cockerels was 6.07 per cent.

Needleman, Herbert L.; and Horwitz, Orville. (*Vascular Sec. of Robinette Foundation, Med. Clinic, Hosp. of the Univ. of Pennsylvania, Philadelphia, Pa.*): A COMPARATIVE STUDY OF THE EFECTS OF THREE VASODILATOR DRUGS, PENTAMETHONIUM BROMIDE (C-5), DILATOL (SKF-1700-A), AND PENDIOMIDE (BA-9295) ON THE DIGITAL CUTENEOUS BLOOD FLOW. Am. J. M. Sc. 226: 164-71, August 1953.

The effects of three vasodilator drugs (pentamethonium bromide or C-5, dilatol or SKF-1700-A, and pendiomide or BA-9295) used intravenously in human subjects were studied under constant environmental conditions by measuring digital cutaneous blood flow, cardiac output, pulse rate, and blood pressure in order to determine their ability to produce selective vasodilatation in the skin of the digits.

C-5 increased the digital cutaneous blood flow in 9 of 14 subjects. It was also a powerful and unpredictable hypotensive agent which increased the cardiac output of 7 of 8 subjects. We presume it dilates vessels in the rest of the body as well as in the skin, but the relative degree of each differs with each person.

SKF-1700-A did not produce any significant increases in the digital cutaneous blood flow but it increased the cardiac output considerably. There were undesirable side-effects, mostly of a sympathomimetic nature. Cardiac arrhythmias were prominent. We presume that it dilates vessels in the skin little or not at all in comparison with those elsewhere.

BA-9295 caused significant increases in the digital cutaneous blood flow in a majority of 10 subjects studied. This was accompanied by only slight hypotension and small increases in the cardiac output. No undesirable side-effects were observed. We presume that this drug causes vasodilatation predominately in skin; therefore, it may be a valuable drug in the treatment of peripheral arterial disease.

Nordlöw, W.; Gronberg, A.; and Svanteson, G. *(Centrallasarettet, Vänersborg, Sweden):* SEX HORMONE TREATMENT IN DIABETIC RETINOPATHY. Nord. Med. *49*:744, May 22, 1953.

Out of 15 males and 12 females with diabetic retinopathy treated with sex hormones, the condition improved in 2, remained unchanged in 13, and deteriorated in 12, the average period of observation being 12.1 months. Cautious evaluation of the results suggests that in the 2 cases which improved, the treatment may possibly have had a beneficial effect.

Oakley, Wilfrid *(King's Coll. Hosp., London, England)*: PROGNOSIS IN DIABETIC PREGNANCY. British Medical Journal *1*:1413-15, June 27, 1953.

Great emphasis must be laid on the importance of the nursing and management of the newborn infant. The use of an isolette in which both oxygen content of the air and temperature can be controlled and regular suction, if there are any signs of respiratory embarrassment, may help to reduce neonatal mortality. Electrolyte and hormone studies are being carried out on these babies in the hope that they may shed some light on the present obscure problem of the high fetal mortality in diabetic pregnancy.

Olson, W. H.; and Necheles, H. *(Med. Res. Inst., Michael Reese Hosp., Chicago, Ill.)*: INITIAL DEPRESSION OF HUMAN GASTRIC SECRETION BY INSULIN. Gastroenterology *24*:362-68, July 1953.

Fifteen adult male patients suffering from duodenal ulcer or from duodenal ulcer symptoms were studied. Gastric basal secretion and secretion following intravenous injection of insulin were determined. The effect of intravenous insulin on gastric secretion was biphasic. The first phase, in most subjects 30 minutes after the injection of insulin, showed a significant depression of acid secreted. This phase coincided with lowest values for blood sugars. The second phase, 60 minutes after insulin in most subjects, showed the well-known stimulation of gastric secretion. The second phase coincided with a rise in the blood sugar curves.

Orbison, J. L.; and Peters, Evelyn *(Inst. of Pathol., Sch. of Med., Western Reserve Univ., Cleveland Ohio):* FAILURE OF RUTIN AND CATECHIN TO AFFECT VASCULAR LESIONS OF EXPERIMENTAL HYPERTENSION OR HYPERSENSITIVITY. Proc. Soc. Exper. Biol. & Med. *83*:173-75, May 1953.

Neither rutin nor catechin altered the vascular lesions of hypersensitivity arteritis in rabbits or of experimental malignant hypertension in dogs.

Padulo, John; and Plotkin, Irv *(Chicago, Ill.)*: DIABETIC NEWS AND VIEWS. CRDA News *41*:10, September 1, 1953.

Slow suicide by obesity is the commonest form of human exodus. But fortunately, when you are overweight, you can make the diagnosis without the doctor's help. An examination in a full-length mirror, a close inspection of the notches in your belt, the fit of your clothes, the remarks of your friends—any or all of these show you whether or not you are the slim person you used to be. Eating is a habit as well as the urge of self preservation. When it goes beyond self preservation, it becomes a bad habit. One sentence will give you the secret of weight reduction and that is, "Nothing makes you fat except food." Glands, heredity and exercise can have an influence on the rate in which you put on that "excessive baggage," but none of these alibi factors can do it alone. Your body can't make fat out of nothing—out of water, air, or any of the odors of your drugstore. Diabetes is sometimes called "fat man's folly!" Why do persons get fat? It certainly can't be strictly from hunger, for the body cannot be crying for the superfluous food thrust upon it, which it has to put into its storeroom. It is the hunger of emotions, not of the stomach. Eating is a sensual satisfaction and you know the feeling of contentment that comes from a full stomach. Unhappiness doesn't seem so intense or worries so important when we are well fed. Like one lonesome fat woman in one of the CRDA stores said, "It's like having company—to eat something."

Pasquinelli, F.; and Calzolari, G. *(1st. di Patol. Gen. dell' Univ. di Firenze, Italia):* ACTION OF INSULIN ON BLOOD AMINO NITROGEN. Enzymologia *16*:125-29, June 15, 1953.

A decrease of glycemia and blood amino nitrogen follows the administration of insulin. The decrease in blood amino nitrogen represents an increase in protein synthesis. The two phenomena are independent of each other, since no correlation was found between the decrease of blood amino nitrogen on the one hand and that of the blood sugar level on the other after administration of different amounts of insulin. These results show that the insulin action on protein synthesis is not a secondary influence following its effect on the glucose metabolism. It has been made probable from analogies to the glucose metabolism that insulin takes part in some transphosphorylation reaction preceeding the constitution of peptide bonds.

Patterson, John W. (*Dept. of Anat., Sch. of Med., Western Reserve Univ., Cleveland*): DEVELOPMENT OF DIABETIC CATARACTS. Am. J. Ophth. 35:68-72, May, Part 2, 1952.

Cataract, one of the complications of diabetes, occurs in young diabetics and is usually bilateral. Although snowflake cataract is the typical cataract found in young diabetics, it is not limited to this disease. The cataracts resulting from parathyroid deficiency, scleroderma and myotonic dystrophy are reported to be indistinguishable from those found in young diabetics. In recent surveys of young diabetic patients, cataracts have been found in 3 to 16 per cent of those examined.

This relationship of cataract to diabetes has also been observed in the experimental animal. The rats used in this study had diabetes produced by the injection of the reversibly oxidized form of vitamin C, dehydroascorbic acid. Certain qualitative observations have been made regarding the relationship of the severity of diabetes to the time of cataract occurrence. Rats with high blood sugar values developed cataracts in 8 to 10 weeks, and both eyes were involved at approximately the same time. Rats with low blood sugar values developed cataracts more slowly, and the lesion was sometimes unilateral or developed in the second eye only after several weeks had elapsed. The time required for diabetic cataract formation was thus related to hyperglycemia.

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dePeyster, F. A.; and Gilchrist, R. K. (*Dept. of Surg., Presbyterian Hosp., Chicago, Ill.*): SURGICAL ASPECTS OF SPONTANEOUS HYPOGLYCEMIA DUE TO OCCULT INSULINOMA. A.M.A. Arch. Surg. 67:330-40, September 1953.

In patients demonstrating Whipple's triad in whom no tumor is found on surgical exploration, it would appear that subtotal pancreatectomy (at least to the right of the superior mesenteric vessels) should be performed. This operation should yield a 75 per cent chance of cure for occult adenomas, based on the distributional incidence of pancreatic insulinomas. Furthermore, subtotal pancreatectomy, according to David, should provide a 50 per cent chance of cure for hypoglycemia due to pancreatic hyperplasia and should benefit two-thirds of the patients with hypoglycemia in whom the resected pancreas is normal.

Phatak, Nilkanth M.; and David, Norman A. (*Depts. of Pharmacol., Univ. of Oregon Med. Sch. and Univ. of Oregon Dental Sch.*): ADDICTION POTENTIALITIES OF SOME METHADONE ANALGESICS AND ALPHA ACETYLMETHADOL AS DETERMINED BY THEIR HYPERGLYCEMIC RESPONSES IN RABBITS. Current Res. in Anesth. & Analg. 32:242-49, July-August 1953.

The methadones and alpha acetylmethadol produce hyperglycemia in rabbits on initial injection. Repeated injections of these compounds produce a tolerance to their hyperglycemic effect. On abrupt withdrawal of administration of such compounds in tolerant animals, hyperglycemia is again evident. The extent of this reappearing withdrawal hyperglycemia seems to be related to the rapidity and intensity of the developed tolerance and may serve as an index of addiction potential in animals.

Prokhovnik, S. J.; and Nelson, J. F. (*Dept. of Physiol., Univ. of Melbourne, Melbourne, Australia*): DETERMINATION OF BLOOD SUGAR WITH ANTHRONE. Australian Exper. Biol. & M. Sc. 31:279-82, June 1953.

The anthrone assay for blood sugar is no quicker than existing methods for this determination. Moreover, it requires a special reagent and the use of a spectrophotometer or absorptiometer for the final measurement. The main advantages of the method lie in its sensitivity and specificity to carbohydrates. It is sensitive to 6 mcg. of glucose, and, hence, as little as 0.01 ml. of blood can

be assayed if necessary. This is often an important consideration in modern physiological experiments with very small animals. The assay has been used for the past six months, and it lends itself particularly to large-scale experiments when a great number of blood sugars need to be determined.

Queries and Minor Notes—Gyland, Stephen (*Tampa, Fla.*): POSSIBLY NEUROGENIC HYPOGLYCEMIA. J.A.M.A. *152*:1184, July 18, 1953.

The history of undue fatigue, nervousness and abnormal craving for sweets, with a normal fasting blood sugar level, indicates hyperinsulinism or so-called neurogenic hypoglycemia. A six-hour glucose tolerance test would no doubt show the hypoglycemia. Regardless of the outcome of the test, the symptoms call for a diet test. Improvement with the proper diet should be spectacular in one or two weeks. This diet is one high in protein, low in carbohydrates and high in fat, with no sweets or caffeine and with frequent feedings.

Rascoff, Henry; Wasser, Seide (*Brooklyn, N. Y.*): POISONING IN A CHILD SIMULATING DIABETIC COMA. J.A.M.A. *152*:1134-35, July 18, 1953.

The authors report a case of "jet beads" berry poisoning in a child with hyperthermia, hyperglycemia, glycosuria and ketonuria, with recovery without use of insulin. These berries contain the glycoside amygdalin, which, when ingested, breaks down into hydrocyanic acid. It was possible that this drug (hydrocyanic acid) has a centric action in the region of the hypothalmus and that, as one has here a glycemic center as well as a heat center, each of these may have been affected by the drug, producing hyperthermia and simultaneously contributing to the hyperglycemia.

Reid, E. (*School of Biochem., Univ. of Cambridge. Now: Emory Univ., Georgia*): ADRENOCORTICOTROPIN IN RELATION TO THE DIABETOGENIC ACTIVITY OF GROWTH-HORMONE PREPARATIONS; FURTHER OBSERVATIONS. J. Endocrinol. 9:322-28, July 1953.

The author had previously demonstrated that in cats, adrenocorticotropin (ACTH) could increase the diabetogenic action of growth hormone (GH) obtained from ox anterior pituitary and that ACTH alone under the test conditions did not have diabetogenic activity. He suggested that a "co-factor" present to a greater extent in crude pituitary extracts could account for this, and his present work appears to show that crude chorionic gonadotropin, semipurified LH and crude "albumin fractions" (by-products of isolation of GH from ox pituitary) could each act as such a "co-factor" which is not yet identifiable but does not appear to be ACTH itself, LH, FSH or crude corticotropin.

Reubi, François C. (*Dept. of Med., Univ. of Berne, Berne, Switzerland*): GLOMERULA FILTRATION RATE, RENAL BLOOD FLOW AND BLOOD VISCOSITY DURING AND AFTER DIABETIC COMA. *Circulation Res. 1*:410-13, September 1953.

Renal functions were studied in nine patients during and after diabetic coma by means of the clearance methods. In four cases, renal extraction of PAH was determined by catheterization of the right renal vein. All patients showed a sharp reduction of urea clearance, glomerular filtration rate, effective renal plasma flow and true renal blood flow at the time of coma. The blood viscosity was markedly increased. Moderate azotemia was present. In eight patients, the disturbed renal functions were promptly restored to normal values after correction of the dehydration. In three of them, renal extraction of PAH was found to be normal, or slightly below normal values, during coma. The slowing down of the renal circulation, which accounts for the azotemia in these eight cases, appears to be due to increased blood viscosity. This condition may be called "functional nephropathy." In the ninth patient, who died from diabetic acidosis and hypokaliemia, we found a decreased renal extraction of PAH, suggesting tubular impairment.

Rindge, Mila E. (*Hartford, Conn.*): EMPLOYMENT OF DIABETICS. Connecticut Health Bull. *67*:215-16, August 1953.

The diabetic seeking employment should be given every consideration, since the controlled diabetic is a good employment risk. With intelligent selective placement of these individuals, they will present no more of a problem than the average worker seeking employment.

According to statistics from the Metropolitan Life In-

surance Company, there are about 250,000 diabetics in the labor force in the United States. Diabetes is essentially a disease of the older worker, that is, the one between 45 and 64. The onset of diabetes of employees in this age group does not constitute a particularly difficult problem in industry since, once the diabetes is under control, the employee is able to carry on much the same as he previously did. However, the diabetic should not be maintained on a job where, through the occurrence of a hypoglycemic reaction, he may endanger his own life or the lives of others.

The Committee on Employment of the American Diabetes Association has formulated suggested standards and procedures for diabetics seeking employment and for employers planning to hire diabetics. Any plant where diabetics are now employed or may be employed would do well to consider these criteria as a basis for drawing up its own standards.

Rose, S. *(Dept. of Physiol., Univ. of Melbourne, Melbourne, Australia):* THE EFFECT OF D.O.C.A. ON DIABETIC KETOSIS. Australian J. Exper. Biol. & M. Sc. *31*:273-78, June 1953.

There is a marked increase in adrenocortical activity in uncontrolled, alloxan-diabetic, ketotic rats. DESOXYCORTICOSTERONE partially suppresses this increased adrenal activity but not to the same extent as insulin control. DOCA administration to diabetic, ketotic rats causes a fall in blood sugar. The fall in blood sugar may be related to the partial suppression of adrenal activitiy and consequent decline in production of 11, 17 oxysteroids. The validity of this causal relationship has been discussed.

Ross, Reinulv *(Oslo, Norway)*: TRANSITORY CHANGES IN THE REFRACTIVE POWER OF THE EYE IN DIABETES. Tidsskrift for den norske laegeforening *15*:587-89, August 1953.

An account is given of the transitory changes in the refractive power of the eye in diabetes. Exacerbation of the metabolic disorder of diabetes has been found to be associated with myopic manifestations, while a reversion of these changes towards a hypermetropia will be observed when the metabolic disorder is brought under control following adequate therapy. The refractive power of the eye usually returns to normal within two to four weeks or, more rarely, within six to seven weeks.

Rothstein, Aser; Meier, Rebecca C.; and Scharff, Thomas G. *(Div. of Pharmacol., Dept. of Radiation Biology, Univ. of Rochester Sch. of Med. and Dent., New York)*: RELATIONSHIP OF CELL SURFACE TO METABOLISM. IX DIGESTION OF PHOSPHORYLATED COMPOUNDS BY ENZYMES LOCATED ON SURFACE OF INTESTINAL CELL. Am. J. Physiol. *173*:41-46, April 1953.

There is little or no direct absorption of glucose phosphate from the small intestine of the rat. However, glucose-I-phosphate is very rapidly hydrolyzed in intestinal loops at a maximal rate of 3.6 mm. per hr. for the entire small intestine. One product, orthophosphate, can be almost completely recovered in the loop. The other product, glucose, can be only partially recovered due to absorption. The rate of hydrolysis of glucose-I-phosphate is about the same in all parts of the small intestine and is the same in excised loops as in *in vivo* loops. In contrast, the absorption of glucose is decreased along the length of the intestine from the stomach to colon and is markedly reduced in excised loops. Eight other phosphate compounds were tested, and all were hydrolyzed to some extent in the intestinal loops. When glucose-I-phosphate with P^{32} incorporated is hydrolyzed, there is no interchange of labeled phosphorus with the phosphate of the intestinal cells, indicating that the hydrolysis is not taking place in the interior of the cells. Phosphatase is not secreted into the loop under the conditions of these experiments. Therefore, it is concluded that the phosphatases are found on the surfaces of the intestinal cells.

St. Amant, A. F. *(Baton Rouge, La.)*: DIABETICS IN PREGNANCY. New Orleans M. & S. J. *104*:660-62, October 1952.

There is no single therapeutic agent which can be used to lower the fetal mortality substantially. Meticulous care and frequent consultation between obstetrician, internist and pediatrician are essential.

Salter, James; and Best, Charles H. *(Toronto, Can.)*: INSULIN AS A GROWTH HORMONE. Brit. M. J. *2*:353-56, August 15, 1953.

Because of the well-known sensitivity of the hypophysectomized animal to the antidiabetic hormone, a slow-acting (protamine zinc-Toronto U-40) insulin was given daily to hypophysectomized rats in increasing

amounts in conjunction with a high carbohydrate diet ad libitum. Hypophysectomized rats receiving protamine zinc insulin ate more and gained more weight than controls; this gain was shown to be associated with an absolute increase in thymus, kidney, heart and liver weights as well as in body fat; and, in addition, tibial tests showed a definite skeletal growth. A second study compared hypophysectomized rats treated with protamine zinc insulin with those receiving an amount of growth hormone which would produce the same amount of growth as in the PZI rats. The PZI rats stored more fat and less water and ate more food (including protein) than the rats treated with growth hormone (GH) but retained a lesser proportion of the ingested protein. The gain in organ size appeared greater in the insulin-treated group. A third study demonstrated epiphyseal disk width to be increased in GH treated rats 154 μ and 75 μ in the PZI group, and, in a normal rat of the same weight as the PZI treated rats, the epiphyseal width was also approximately 75 μ.

The authors suggest that insulin may be one of the missing factors in the pituitary dwarfs and that insulin production may be restricted enough to prevent growth without producing diabetes.

Segaloff, Albert; and Horwitt, Benjamin N. (*Dept. of Med., Tulane Univ. Sch. of Med. and the Endocrine Res. Lab. of the Alton Ochsner Med. Foundation, New Orleans, La.*): THE INFLUENCE OF EPI-F, A STEREOISOMER OF COMPOUND F, ON THE GLYCOGENIC PROPERTY OF COMPOUND F (17-HYDROXYCORTICOSTERONE). Science 118:220-21, August 21, 1953.

In view of the well-established antagonistic action of structural analogs, the authors studied the relative glycogenic activities of compound F; of its streoisomer, epi-F, and of mixtures of the two compounds when administered to adrenalectomized mice. The expected substantial deposition of glycogen was obtained with compound F. Limited glycogen deposition occurred with epi-F. Mixtures of epi-F and F in ratios of 5:1 and 25:1 resulted in no apparent effect on the glycogen deposition obtained with compound F.

Sindoni, Anthony, Jr. (*Philadelphia, Pa.*): THE ROLE OF THE CHIROPODIST IN DIABETES. Delaware M. J. 25:132-33, June 1953.

Chiropodists, today, must take their place among those doctors who will help discover the existence of diabetes as well as help to prevent vascular disorders of the lower extremities in the diabetic. No sacrifice is too great to help combat the increasing prevalence of peripheral vascular disease in diabetes. This can be accomplished by the co-ordination of various branches of medicine, including modern chiropody.

Sindoni, Anthony, Jr.; Gerber, Philip; Bove, Frank; and Zibold, Louise (*Philadelphia Genl. Hosp., Philadelphia, Pa.*): COMPATIBLE HYPERGLYCEMIA. Am. J. Digest. Dis. 20:157-78, June 1953.

The postprandial blood sugar level for the diabetic which is most "compatible" to his well-being depends upon (1) age, (2) condition of the cardiovascular system, (3) occupation, (4) existing complications, (5) insulin and (6) activities. This "compatible" postprandial level in patients taking insulin is generally considered to be 170-222 mg. per 100 cc. of whole blood. If the patient is not upon insulin, the "compatible" blood sugar level may be lower. This may exist with or without glycosuria.

Sinex, F. Marott; Macmullen, Jean; and Hastings, A. Baird (*Dept. of Biol. Chem., Harvard Med. Sch., Boston, Mass., and the Biochemistry Div. of the Med. Dept., Brookhaven National Lab., Upton, N. Y.*): THE EFFECT OF INSULIN ON THE INCORPORATION OF C^{14} INTO THE PROTEIN OF RAT DIAPHRAGM. J. Biol. Chem. 198:615-19, October 1952.

Insulin increased the incorporation of C^{14} from carboxyl-labeled DL-alanine into the protein of rat diaphragm *in vitro* in the absence of added substrates. Pyruvate markedly decreased the incorporation of C^{14} alanine into diaphragm protein. Glucose produced a slight decrease in the incorporation. In the presence of these added substrates, insulin had only slight effects. From these results, the authors suggest that a description of the metabolic activity of insulin should include an explanation for its stimulatory activity on the incorporation of alanine into protein, an activity apparently not dependent upon an increased conversion of glucose to glucose-6-phosphate.

Sinkoff, M. W.; and de Bodo, R. C. (*Dept. of Pharm., New York Univ. Coll. of Med., New York City*): PROLACTIN AS IN INSULIN ANTAGONIST. Arch. exper. Path. u Pharmakol. *219*:100-10, May 1953.

Prolactin in dosages of 1 to 5 mg. per kg. per day produced an anti-insulin action in hypophysectomized dogs, that is, it diminished the exaggerated insulin response of these animals. It concomitantly diminished the secondary hypoglycemia of the glucose tolerance test without producing diabetes mellitus. These actions were not so marked as those of growth hormone in comparable dosages. It is suggested that the anti-insulin action of either prolactin or growth hormone (a) is an intrinsic property of the hormone or (b) is due to the action of another independent hormone of the anterior pituitary, viz., the "anti-insulin" or "diabetogenic" factor, parts of which are mixed with the prolactin and growth hormone preparations presently available.

Sirek, Otakar V.; and Best, Charles H. (*Banting and Best Dept. of Med. Res., Univ. of Toronto, Canada*): THE PROTEIN ANABOLIC EFFECT OF TESTOSTERONE PROPIONATE AND ITS RELATIONSHIP TO INSULIN. Endocrinology *52*:390-95, April 1953.

The behavior of the N.P.N. level under the influence of the male sex hormone, testosterone propionate, in the normal and diabetic dog indicates very strongly that the protein anabolic effect of the male sex hormone is intimately associated with the presence of insulin in the body. The fact that testosterone failed to exhibit any influence upon the blood sugar of the normal dog does not oppose the evidence indicating that certain physiological amounts of insulin must be available to the body if testosterone is to exhibit any protein anabolic function. There is not, however, any indication from these experiments that testosterone propionate causes a detectable increase in the amount of insulin liberated from the pancreas. As yet, little is known about the mechanism by which testosterone produces the protein anabolic effect for which the presence of insulin appears to be necessary.

Skillern, Penn G.; and Rynearson, E. H. (*Div. of Med., Cleveland Clin., Cleveland, Ohio, and Div. of Med., Mayo Clinic, Rochester, Minn.*): MEDICAL ASPECTS OF HYPOGLYCEMIA. J. Clin. Endocrinol. and Metab. *13*:587-603, May 1953.

In this discussion there has been an attempt to emphasize the importance of separating hyperinsulinism from all other types of hypoglycemia. If hyperinsulinism is suspected and diagnosed, the patient's life may be saved by surgical treatment. If spontaneous hypoglycemia has been erroneously diagnosed, the physician may aid many patients by disproving the diagnosis; if spontaneous hypoglycemia is proved to be present, the patient may be benefited by dietary management.

Smith, Durwood J. (*Dept. Med. Univ. of Rochester Sch. of Med. and Dent., Med. Clins., Strong Memorial and Rochester Municipal Hosps., Rochester, N. Y.*): VARIATIONS IN VASCULAR REACTIVITY PRODUCED BY SEASON, COLD STRESS AND IMMATURITY; ROLE OF THYROID AND ADRENAL CORTEX. Am. J. Physiol. *172*:118-28, January 1953.

The author describes seasonal variations in the reactions of isolated adult swine carotid arteries when studied by an angioplethysmokymographic technic. In winter (November through April), the reactions to epinephrine and acetylcholine are shorter and the reaction to histamine is more marked than in summer. The arteries of young swine ($\angle$ 12 kg.) have a pattern of reactivity similar to the winter-killed adult swine. The arteries of thyroidectomized swine showed the same pattern of reactivity as the adult winter-killed swine and the immature swine ($\angle$ 12 kg.). This pattern reverted to normal when *dl*-thyroxine was added to the perfusate. The arteries of acutely cold-stressed pigs showed a prolonged reaction to histamine which, however, did not duplicate the curve of the winter-killed adult swine. There was no change in the response to acetylcholine. The epinephrine response was not studied. The histamine response in the arteries of adrenalectomized pigs was prolonged; cortisone shortened this reaction. There was no significant change in the reaction to epinephrine or acetylcholine. Inhibition of amine oxidase, cholinesterase and histaminase resulted in an increase in the percentage vasoconstriction and the reaction time of isolated arteries to l-epinephrine, acetylcholine and histamine respectively. The role of the thyroid in these responses is discussed; in general, the physiologic status during the winter months corresponds to a hypothyroid state.

Sokolov, R. A.; and McKean, R. M. (*Harper Hosp., Detroit, Mich.*): DIABETIC COMA AT HARPER HOSPITAL, 1947-1951. Harper Hosp. Bull. *11*:197-201, September-October 1953.

In a review of 37 cases of diabetic coma admitted to Harper Hospital during the five-year period from 1947-1951, it appeared that on the average, the cases seemed more severe than in many institutions. The corrected mortality was 21 per cent.

Spitzer, John J. (*Dept. of Physiol., Florida State Univ., Tallahassee, Fla.*): INFLUENCE OF PROTAMINE ON ALIMENTARY LIPEMIA. Am. J. Physiol. *174*:43-45, July 1953.

Intravenous administration of protamine to dogs showing alimentary lipemia causes an increase in the visible lipemia. This effect can be repeated several times. Protamine is effective only when some visible lipemia is still present, no matter how weak this is. No such effect can be produced in normal fasting dogs. Protamine proved to be effective only *in vivo*. The change in lipemia produced by protamine sets in very slowly, having a maximum about 30-40 minutes after the injection, which is in contrast to the instantaneous anticoagulant neutralizing property of protamine. Protamine fails to produce any visible change in lipemia when administered after the injection of lipase. These observations, together with the fact that two other antiheparin substances—namely, toluidine blue and neutral red—failed to influence visible lipemia, suggest that the effect of protamine is a *sui generis* action rather than a consequence of its antiheparin property.

Sprague, Randall G.; and Power, Marschelle H. (*Rochester, Minn.*): ELECTROLYTE METABOLISM IN DIABETIC ACIDOSIS. J.A.M.A. *151*:970-76, March 21, 1953.

Conventional treatment with insulin, water and sodium chloride, with or without glucose, may induce important disturbances in the electrolyte composition of the extracellular and intracellular fluid in addition to those that are present before therapy is begun. It can now be anticipated that reasonably accurate replacement of water and electrolytes will save some patients in diabetic acidosis who otherwise would die.

Clinically, it is after several hours of treatment of diabetic acidosis that difficulties due to potassium deficiency begin to make their appearance. A low level of serum potassium may or may not be associated with symptoms of potassium deficiency. Perhaps the magnitude of the antecedent loss of potassium is as significant a factor as the concentration of potassium in the extracellular fluid. Even in the absence of frank symptoms, it seems likely that potassium deficiency may delay the return of normal health and vigor. One gains the impression that clinical recovery from the effects of severe diabetic acidosis is accelerated in those patients to whom potassium is administered.

It is neither necessary nor safe to administer potassium in the early hours of treatment while the concentration of potassium in the blood serum is elevated or normal. It has been our practice to start administration of potassium approximately four hours after the initiation of therapy, provided that the output of urine is satisfactory. By then, almost uniformly, the concentration of potassium in the serum has decreased significantly.

The deficiency of phosphorus is of such large magnitude that it would seem desirable to correct it. Both potassium and phosphate may be supplied at a rate of about 20 to 25 mEq. per hour in the form of a buffered solution of monobasic and dibasic potassium phosphate. Administration may be started approximately four hours after the initiation of treatment of diabetic acidosis.

Loss of sodium chloride is a prominent factor in the dehydration vascular collapse, renal insufficiency and coma that characterize severe diabetic acidosism, and replacement is imperative. If hyperchloremia is permitted to develop because of administration of excess amounts of chloride ion, correction of acidosis will be delayed. In extreme cases after several hours of vigorous treatment, acidosis that initially was due chiefly to accumulation of excessive amounts of ketone acids may be replaced by acidosis due to accumulation of excessive amounts of chloride (so-called chloride acidosis). The persistence of acidosis prolongs hyperpnea unnecessarily and may interefere with the action of insulin.

A solution that may be preferable can be prepared by mixing 650 cc. of isotonic solution of sodium chloride, 50 cc. of a solution containing 44.6 mEq. each of sodium and bicarbonate, and 300 cc. of distilled water. This solution contains 142 mEq. of sodium and 97.5 mEq. of chloride per liter.

The loss of water may be extreme, amounting to 10 per cent or more of body weight. Clinically, severe dehydration is a conspicuous feature. Replacement of lost water is obviously necessary for correction of shock, if this exists, and restoration of renal function. Fluids and other treatment may fail to prevent or correct circulatory collapse. Estimations of the hematocrit reading before treatment and periodically during the early hours of treatment may help in the early recognition of shock, or the lack of response of existing shock to treatment.

Failure of the cell volume to fall 5 to 10 per cent in the first few hours of treatment with adequate amounts of intravenous fluid and electrolytes indicates that the desired dilution of the blood is not occurring because too much of the administered fluid is leaving the circulation. Transfusions of plasma or whole blood may help to correct this serious situation. The possibility of overhydration must receive consideration. This is not likely to occur in the first few hours of treatment. Later, however, attention to certain signs will help to avert serious overhydration; namely, râles indicative of moisture in the bases of the lungs, a low output of urine in spite of administration of a large volume pressure.

Accurate replacement of losses of water and electrolytes, while advantageous, still cannot be expected to prevent some fatalities among patients who are in irreversible shock or who have serious complicating illnesses.

Steiner, Mathew M. (*Chicago, Ill.*): GALACTOSEMIA AND GALACTOSURIA. Am. J. Ophth. *36*:841-43, June 1953.

The subject of galactose diabetes is discussed, with the presentation of a case report.

Stewart, Ronald D.; and Roitman, Ellen (*Dalhousie Univ., Halifax, Nova Scotia*): EFFECT OF PANCREATIC EXTRACTS ON KETONE BODY PRODUCTION OF RAT LIVER. Endocrinology *53*:192-97, August 1953.

The present study was an endeavor to prepare an "antiketogenic" extract from the pancreas and correlate this property with its hyperglycemic-glycogenolytic factor (HGF) by determining the ketone body formation of rat liver slices both with and without the addition of crude anterior pituitary extract. The extract as prepared by the authors caused on the average a 30 per cent reduction in ketone body output of rat liver slices when in the presence of crude anterior pituitary extract likewise prepared by the authors and would also cause a 20 to 30 per cent increase in blood sugar in fed rabbits when injected intravenously, but no effect was noted in fasting rabbits so injected.

Stadie, William C.; Haugaard, Niels; and Vaughan, Martha (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): STUDIES OF INSULIN BINDING WITH ISOTOPICALLY LABELED INSULIN. J. Biol. Chem. *199*:729-39, December 1952.

Methods for the preparation and quantitative determination of insulin labeled with S^{35} and I^{131} are described. The binding of these radioactive insulin preparations to rat diaphragm under a variety of experimental conditions was determined. Types of experiments indicating that the combination is of chemical character are reported and the significance of the findings is discussed.

Stadie, William C.; Haugaard, Niels; and Marsh, Julian B. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): THE EFFECT OF GROWTH HORMONE AND CORTISONE ON THE ACTION OF BOUND INSULIN. J. Biol. Chem. *198*:785-90, October 1952.

The authors report that, with the action of bound insulin as a criterion, they were able to show that the isolated rat diaphragm of the hypophysectomized rat synthesizes an extra amount of glycogen. This is considered to be in accord with the well-known "hypersensitivity" of the hypophysectomized animal to insulin. Adrenalectomy produced no change. In the case of hypophysectomized and adrenalectomized rats, prior injection of *both* growth hormone preparation and cortisone was required to decrease the accelerating action of bound insulin as measured by the glycogen synthesis by rat diaphragms *in vitro*. The signficance of these findings, particularly the synergy of growth hormone and cortisone in opposing insulin action, is discussed.

Stahl, J.; and Dorner, M. (*Paris, France*): RESEARCH ON THE ORIGIN OF THE PANCREATIC HYPERGLYCEMIC PRINCIPLE. Comptes Rendus, Société de Biologie *146*:1782-85, July 11, 1952.

A hyperglycemic principle exists in the pancreas, the effect of which manifests itself before that of insulin. This principle remains active after inactivation of insulin through alkalization. It is still found in extracts of pancreas after degeneration of their exocrine acini and after destruction of the beta cells of the islands of Langerhans (alloxan, Young's diabetes). Therefore, it seems very probable that the hyperglycemic substance comes from the alpha cells.

Steine, Lyon. (*Valley Stream, N. Y.*): SIMPLE OFFICE TREATMENT OF DIABETES. GP *8*:45-47, July 1953.

Information should be given to the patient about the nature of diabetes and how it can be kept under control so that he can live a normal life with a normal life span.

Story, Robert D.; and Sagild, Uffe (*Boston, Mass.*): WHIPPLE'S DISEASE (INTESTINAL LIPODYSTROPHY) AND SERUM GLYCOPROTEINS. J.A.M.A. *152*:312-17, May 23, 1953.

Whipple, in 1907, described a disease characterized clinically by vague abdominal distress, steatorrhea, progressive loss of weight and strength, and arthralgia. Almost all patients are middle-aged men. Frequently there is a brown pigmentation of the skin and hypotension, suggesting Addison's disease. The course of the disease is occasionally febrile and there may be generalized lymphadenopathy, suggesting infection. Death usually occurs one to five years after the onset of symptoms. Almost invariably laboratory examinations disclose steatorrhea, secondary anemia and hypoproteinemia. A normal or flat dextrose tolerance curve, achlorhydria and hypocalcemia are frequently found, and occasionally persistent leukocytosis or eosinophilia is noted. Results of adrenocortical function tests are usually normal. X-ray studies of the small intestine frequently reveal a so-called deficiency pattern.

A case of Whipple's disease that was diagnosed *ante mortem* is presented. The markedly elevated glycoproteins of the serum, hitherto undescribed, may have some pathogenic relationship to the glycoprotein-laden macrophages that characterize Whipple's disease histologically. The patient had a diabetic glucose tolerance curve, which is unusual in Whipple's disease.

Strisower, E. H.; Kohler, G. D.; and Chaikoff, I. L. (*Div. of Physiol. of the Univ. of California Sch. of Med., Berkeley, Calif.*): INCORPORATION OF ACETATE CARBON INTO GLUCOSE BY LIVER SLICES FROM NORMAL AND ALLOXAN-DIABETIC RATS. J. Biol. Chem. *198*:115-26, September 1952.

The investigation deals with the conversion of acetate to glucose by surviving rat liver slices. Normal and diabetic liver slices incorporated about 5 per cent of the added C^{14} from carboxyl-labeled acetate into glucose and 15 to 20 per cent from methyl-labeled acetate. Incorporation of acetate carbon into glucose by liver was greatly reduced when diabetic rats were injected with insulin. An explanation of the results is offered which is based on the effect of isotope dilution upon the limits of isotope patterns attained by compounds in the tricarboxylic acid cycle.

Svanteson, Gunnar *(Centrallasarettet, Vänersborg, Sweden):* DIABETES MELLITUS AND PREGNANCY. Nord. Med. *49*:536, April 10, 1953.

During the years 1947-1952, fifteen cases of pregnancy associated with diabetes were treated on the following principles: (1) Careful checks on the diabetes and pregnancy; (2) Delivery by cesarean section in the thirty-first week, one with hydramnios in the thirty-children's department immediately after delivery. Eleven mothers were delivered by cesarean section, one of them twice. Three were delivered spontaneously (one with hydramnios and highly macerated stillborn fetus in the thirty-first week, one with hydramnios in the thirty-fifth week, and one premature delivery in the thirty-sixth week). All mothers survived. Two of them had hydramnios and two slight albuminuria. One had severe retinopathy, which healed fully during pregnancy. In none of the fourteen live births did the infants present any deformities, and all of them were clinically symptom-free on discharge.

Swell, Leon; and Flick, D. F. (*Genl. Med. Res. Lab., Veterans Administration Cent., Martinsburg, W. Va.*): EFFECT OF DIETARY FAT AND CHOLESTEROL ON THE BLOOD CHOLESTEROL LEVEL IN RATS. Am. J. Physiol. *174*:51-53, July 1953.

Rats were fed diets containing 25 per cent lard, oleic acid or stearic acid diets with and without cholesterol. The blood cholesterol rose sharply in both groups on the lard diets. The change occurred predominantly in the ester fraction. When oleic acid was added to the diets, the total and ester cholesterol of both groups declined slightly. On the stearic acid diets, the total and ester cholesterol of both groups declined, but more sharply in the cholesterol group. It is suggested that incomplete absorption of cholesterol takes place when a high percentage of saturated fatty acid is present in the diet.

Takata, Maki; Takahashi, Yoshiyasu; and Sasaki, K. (*Univ. of Tokyo, Tokyo, Japan*): A NEW MICRO-METHOD FOR DETERMINATION OF BLOOD SUGAR (PERIODATE METHOD). Klinische Wochenschrift *31*:590-93, July 1, 1953.

The blood sugar level is determined not by the generally common method of using the reducing properties of sugar but through periodate oxidation of the sugar substances.

Tidwell, Herbert C.; Nagler, Mary E.; Dunkelberg, Carolyn (*Dept. of Biochemistry, Southwestern Med. Sch. of the Univ. of Texas, Dallas, Tex.*): TISSUE GLYCOGEN STORAGE AS AFFECTED BY ACETOACETATE. Proc. Soc. Exper. Biol. & Med. 82:649-52, April 1953.

Glycogen contents of rat liver and leg muscle were unchanged after daily injection of acetoacetate and propionate in increasing amounts for 21 weeks. Ability of very small amounts of insulin to promote glycogenesis in surviving hemidiaphragms was not inhibited by 50 mg. per cent of acetoacetate. A rapid hydrolysis of the glycogen of liver slices was unaffected by 125 mg. per cent of acetoacetate in the buffer in the absence of glycose, but glycogenolysis was markedly decreased if both were present. Acetoacetate in these concentrations does not appear to inactivate insulin, to inhibit glycogen storage in the muscle or liver tissue, or to affect appreciably the utilization of carbohydrate as measured by the glucose tolerance.

Treadwell, Carleton R.; and Dury, Abraham (*Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Pa.*): EPINEPHINE AND INSULIN EFFECT ON POTASSIUM MOBILIZATION: RELATIONSHIP OF LIPID AND CARBOHYDRATE METABOLISM. Proc. Soc. Exper. Biol. & Med. 82:727-30, April 1953.

The effects of epinephrine and of insulin pretreatment on liver lipid partition, glycogen, water and electrolyte content, and certain plasma constituents were compared in adrenalectomized-alloxanized groups of rats given a glucose infusion. A similar pattern of changes in liver lipid partition was found in both pretreated groups compared with the nonpretreated controls. An increased liver potassium and lowered plasma potassium content was found in both pretreated groups. However, differences in liver glycogen content and glycemic level in the pretreated groups were sufficiently notable to suggest that common resultant effects on potassium mobilization probably were not produced by the same mechanism of action of both hormones.

Udenfriend, Sidney; Cooper, Jack R.; Clark, Carroll T.; and Baer, John E. (*Lab. of Chem. Pharmacology, Natl. Heart Inst., Natl. Insts. of Health, U.S.P.H.S., U.S. Dept. of Health, Education, and Welfare, Bethesda, Md.*): RATE OF TURNOVER OF EPINEPHRINE IN THE ADRENAL MEDULLA. Science 117:663-65, June 12, 1953.

Studies with C^{14}-labeled phenyl-alanine or tryosine administered orally or intraperitoneally to rats or rabbits indicate that the rate of formation and the rate of secretion of adrenal epinephrine are extremely slow. After the administration of labeled phenylalanine, the resulting adrenal epinephrine was found in rats to have a half life of about 9 days. A confirmatory study in rabbits employing a chemical method of analysis revealed that half of the epinephrine which disappeared from the adrenal glands after insulin injections was restored in 72 hours. No measurable quantities of nor-epinephrine were found in the glands at any time.

Van Beek, Mej. C. (*Leiden, Netherlands*): PATHOGENESIS OF DIABETES MELLITUS. Maandschrift voor Kindergeneeskunde 19:85, May 1951. (Abstracted from Am. J. Dis. Child 86:107-08, July 1953.)

An historical review of the pathogenesis of diabetes mellitus is given.

Vickery, Robert D. (*Omaha, Neb.*): THE OCULAR COMPLICATIONS OF DIABETES MELLITUS. Nebraska M. J. 37:354-56, November 1952.

The author points out the increasing incidence of diabetic retinopathy, relating it to the length of time the disease has been present rather than to the blood sugar levels. Other eye complications of diabetes mellitus, such as cataract, rubeosis of the iris, soft eyeball of coma, pathologic lipemia and so on are briefly considered, and the treatment is discussed.

Volk, Bruno W.; and Lazarus, Sydney S. (*Div. of Labs., Jewish Sanitarium and Hosp., for Chronic Dis., Brooklyn, N. Y.*): METABOLIC EFFECTS OF GROWTH IN FASTING, PHLORHIZINIZED AND ADRENALECTOMIZED RATS. Proc. Soc. Exper. Biol. & Med. 83:151-54, May 1953.

Growth hormone causes a marked reduction in urinary nitrogen output in the fasted phlorhizinized normal rat but does not have this effect in either the phlorhizinized adrenalectomized or the unphlorhizinized normal or adrenalectomized animal. In view of the ketogenic effect of growth hormone in the normal fasted rat and the absence of this effect in either the adrenalectomized, the phlorhizinized normal, or the phlorhizinized adrenalec-

tomized rat, the hypothesis is advanced that the ketogenic action of growth hormone is independent of its nitrogen-retaining action and apparently requires the presence of the adrenal cortex for its appearance. Growth hormone caused a marked reduction of glycosuria in the phlorhizinized fasted rat. This together with the reported increased glycosuria of alloxanized or ACTH-treated rats after growth hormone lead to the conclusion that the diabetogenic action of growth hormone is indicative of a relative preponderance of the inhibitory action of growth hormone on peripheral glucose uptake over its action in reducing gluconeogenesis from protein in the liver.

Waddell, William R.; Geyer, Robert P.; Saslaw, Irving M.; and Stare, Fredrick J. (*Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.*): NORMAL DISAPPEARANCE CURVE OF EMULSIFIED FAT FROM THE BLOOD STREAM AND SOME FACTORS WHICH INFLUENCE IT. Am. J. Physiol. *174*:39-42, July 1953.

Using a simple turbidimetric method for determining blood fat after infusion of fat emulsion, the authors studied the effects of various emulsifying systems, types of oil, blood fat concentration, *p*H, and titratable acidity upon the clearance of emulsified fat from blood stream of rats. Neither the *p*H nor the titratable acidity of the various preparations correlated with the rate at which the fat was cleared. Except where gelatin was used as the emulsifying agent, the rate of disappearance of emulsified fat from the blood indicated a first-order process. The absolute rate of clearance of triglyceride oils is not influenced by the chemical composition of oil in the emulsion but is influenced by the emulsifying agents used.

Ward, O. Conor (*Dept. of Child Health, Alder Hey Children's Hosp., Liverpool, England*): BLOOD SUGAR STUDIES ON PREMATURE BABIES. Arch. Dis. Childhood 28:194-97, June 1953.

The blood sugar has been studied in premature babies in the first two days of life. Low levels have been found, but these were not associated with abnormal symptoms. It is suggested that they are due to a low liver glycogen content, which is depleted by starvation. The endocrine control of the blood sugar in premature babies is discussed.

Warming-Larsen, Aage (*Med. Dept. III, Kommunehospitalet, Copenhagen and Med. Dept., Blegdamshospitalet, Copenhagen, Denmark*): RENAL EXCRETION OF KETONE BODIES II. Acta medica Scandinavica *164*:197-200, December 10, 1952.

Fifteen normal persons were studied during fasting periods of various lengths, and the amounts of betahydroxybutyric acid filtered, excreted and reabsorbed were determined. An active reabsorption of beta-hydroxybutyric acid in the kidney tubules was demonstrated. With increasing amounts of beta-hydroxybutyric acid filtered, there was an increase in the amount absorbed up to a certain limit beyond which the reabsorption rate of beta-hydroxybutyric acid was fairly constant at from 20 to 28 mg. per minute.

Weinstein, Albert (*Vanderbilt Univ. Sch. of Med., Nashville, Tenn.*): PREGNANCY IN THE DIABETIC. Am. Pract. *4*:384-89, June 1953.

This article is a review of the current literature on the treatment of pregnancy complicated by diabetes.

If laboratory facilities permit the determination of serum gonadotroph levels and the urinary excretion of pregnandiol, a warning of impending toxemia may be had; and when measurable evidence of forthcoming toxemia is obtained, stilbestrol should be used. If stilbestrol is given routinely to all diabetic women, more than half will receive stilbestrol unnecessarily.

Each community of any size should arrange a central laboratory capable of performing the indicated hormone assays; and the pediatrician should have an aggressive preconceived routine for safeguarding the newborn. This in itself will improve neonatal survival materially.

Diabetic women are justified in seeking a normal home life with children as a part of the picture if good medical, obstetric, and pediatric care can be had and if the father has a family background singularly free of a diabetic inheritance.

Weller, Charles; and Liccione, William (*Div. of Int. Med., Grasslands Hosp., Valhalla, N. Y.*): FAILURE OF HYALURONIDASE TO INCREASE THE RATE OF ABSORPTION OF DEPOT INSULIN. New York State J. Med. 52:2015-16, August 15, 1952.

Mixtures containing the spreading factor, hyaluronidase, with depot insulins were not found to cause any significant effect in enhancing the rapidity or intensity of effect of depot insulins in normoglycemic individuals.

Welt, Isaac D.; DeWitt, Stetten, Jr.; Ingle, Dwight J.; and Morley, Erving H. (*Div. of Nutrit. and Physiol., The Pub. Health Res. Inst. of the City of New York, Inc., New York, N. Y., and the Res. Lab., The Upjohn Co., Kalamazoo, Mich.*): EFFECT OF CORTISONE UPON RATES OF GLUCOSE PRODUCTION AND OXIDATION IN THE RAT. J. Biol. Chem. *197*:57-66, July 1952.

By means of continuous intravenous injection of a solution of C^{14} glucose into anesthetized rats, the authors were able to attain constant levels of specific activity of urinary glucose in normal and cortisone-treated rats. From the specific activities of injected and excreted glucose and the known rate of injection, the rate of formation of glucose from sources not derived from the infused glucose was calculated. Treatment with cortisone resulted in an approximately sevenfold increase over normal in this rate of gluconeogenesis as compared with a twofold increase observed in alloxan diabetes. The rate of oxidation of glucose to carbon dioxide in the rat did not appear to be greatly affected by pretreatment with cortisone. A far smaller fraction of liver glycogen was formed from body glucose in the cortisone-treated rat than in the normal rat. The authors conclude that the rate of glucose production by the rat is, within the limits studied, essentially independent of the rate of glucose injection.

White, Raleigh R. (*Dept. of Surg., Scott and White Clin., Temple, Tex.*): ORGANIC HYPERINSULINISM; SURGICAL MANAGEMENT. South. M. J. *46*:169-74, February 1953.

The author reviews, by case presentation, problems related to the diagnosis and surgical management of organic hyperinsulinism, classified under the categories of (a) adenoma (b) carcinoma and (c) hyperplasia of islet cells. The importance is stressed of establishing the diagnosis and performing surgery prior to the occurrence of irreversible brain damage. The author points out that multiple adenomas occur in 12 per cent of cases. He also recommends massive subtotal resection of the pancreas in the event that no tumor or adenoma is found at the time of surgical exploration and emphasizes that careful microscopic study of serial sections of the excised gland may be required to demonstrate either an adenoma or hyperplastic islets.

Whitely, James M.; Adams, Theodore W.; and Parrott, Max H. (*Portland, Ore.*): DIABETES AND PREGNANCY. West. J. Surg. *61*:439-47, August 1953.

The authors report on 72 diabetic pregnancies which were concluded at the Good Samaritan Hospital in Portland, Ore., from January 1, 1941, through July 1, 1952. The over-all fetal mortality in the series was 19.4 per cent. Fetal mortality is compared with time of delivery, method of delivery, diabetic control, severity of diabetes and duration of diabetes.

Wick, Arne N.; and Drury, Douglas R. (*Scripps Metabolic Clin., La Jolla, Calif., Univ. of Southern California, Los Angeles, Calif.*): ALTERATION OF THE ACTION OF INSULIN ON GLUCOSE METABOLISM BY BETA-HYDROXYBUTYRIC ACID. Am. J. Med. *13*:101, July 1952 (Abstract of paper presented at the Fifth Annual Meeting of the Western Society for Clinical Research, Carmel, Calif., January 25 and 26, 1952.)

Eviscerated rabbits were given maximal dosages of insulin and just enough C^{14} labeled glucose to maintain the blood sugar at a normal level for eight hours. The carbon dioxide was collected for radioactivity determination. For the first five hours insulin and glucose were given; and then, for three hours in addition to these, beta-hydroxybutyric acid had little effect on the glucose oxidation and requirement. The addition of beta-hydroxybutyric acid had little effect on the glucose requirement, but there was a marked decrease in the amount of glucose oxidized. These results are interpreted to indicate that beta-hydroxybutyric acid does not affect the action of insulin in transferring glucose into the cells but does compete with glucose for terminal oxidation within the cell.

Wick, Arne N.; and Drury, Douglas R. (*Scripps Metabolic Clin., La Jolla, Calif., and the Dept. of Physiol., Univ. of Southern California, Los Angeles, Calif.*): ACTION OF INSULIN ON VOLUME OF DISTRIBUTION OF GALACTOSE IN THE BODY. Am. J. Physiol. *173*:229-32, May 1953.

The effect of insulin on the volume of distribution and oxidation of D-galactose-l-C^{14} has been studied in the extrahepatic tissues of the rabbit with the following results: (a) There is a small but definite oxidation of galactose by the extrahepatic tissues. (b) Insulin accelerates the rate of entry of galactose into the cells of the extrahepatic tissues. (c) The transfer of galactose into the cell cannot be the result of a physical process like diffusion, but must be brought about by some specific

reaction like a chemical process. (d) Glucose and galactose compete in entering into the reaction controlled by insulin.

Wilkerson, Hugh L. C.; and Krall, Leo P. (*Boston, Mass.*): DIABETES IN A NEW ENGLAND TOWN. J.A.M.A. *152*:1322-28, August 1, 1953.

In the winter of 1946-1947, a diabetes survey was made of 70.6 per cent of the entire population of 4,983 persons in Oxford, Mass. A follow-up study in Oxford was conducted in the winter of 1950-1951.

There were three persons, two aged 35 and one 36 respectively, who originally had borderline blood sugar values around 140 mg. per 100 cc.; they had now become definitely diabetic. The high incidence of diabetes in the suspect group indicates that persons with relatively high but not diagnostic blood sugar levels should be periodically re-examined. Patients who have "a little sugar in the urine" or blood sugar "a little higher than normal" are the future diabetics. Whatever preventive measures are available could be best focused on these cases of near diabetes. The four-year diabetes follow-up study was made of the following groups selected from those persons tested for diabetes in the original survey: 70 diabetics identified in 1946-1947; a blood sugar suspect group of 118 with borderline or relatively higher than normal blood sugar readings in the original survey; a control group of 225 with average or normal blood sugar readings in the original survey; and a suspect group of 17 with repeated glycosuria. In 62 of the 70 diabetics observed in the original survey, the classification of diabetes was justified on follow-up. In seven of the other eight cases currently failing to meet criteria for diabetes, there exists the possibility of remission of mild diabetes, but they are subject to question. Among a group of 17 persons with unclassified glycosuria in the original survey, 4 have become diabetic in the four-year interval. (Of these diabetics, three were included also in the blood sugar suspect group.) This suggests that the allegedly harmless glycosurias may often hide incipient diabetes.

Some of the severest degenerative sequelae appeared to be present in the patients with the poorest degree of control, although this could not be definitely proved at this time.

Winternitz, W. W.; and Long, C. N. H. (*Dept. of Physiology, Yale Univ., New Haven, Conn.*): PARTICIPATION OF ADRENAL CORTEX IN ALTERATIONS IN CARBOHYDRATE METABOLISM PRODUCED BY EPINEPHRINE. Proc. Soc. Exper. Biol. & Med. *81*:683-85, December 1952.

The subcutaneous injection of epinephrine (0.02 mg. per 100 gm. of body weight) into fasted adrenalectomized rats is followed by a twofold greater loss of muscle glycogen than in intact rats and by little or no increase in liver glycogen. Consequently, there is a sixfold greater disappearance of carbohydrate from the body that is not accounted for by the accumulation of glucose or lactic acid in the body fluids. The injection of large quantities of adrenal cortical extract prior to and during the period of epinephrine action brings about a restoration of the carbohydrate balance to that found in intact rats.

Winters, R. W.; Schultz, R. B.; and Krehl, W. A. (*Yale Nutrition Lab., Yale Univ. Sch. of Med., New Haven, Conn.*): THE ADRENAL CORTEX OF THE PANTOTHENIC ACID-DEFICIENT RAT: CARBOHYDRATE METABOLISM. Endocrinology *50*:388-98, April 1952.

Pantothenic acid-deficient (5 to 6 weeks) and pair-fed control rats were studied with respect to certain aspects of carbohydrate metabolism in order to gain further insight into the adrenal insufficiency which these animals demonstrate. The deficient animals were found to have an increase in their sensitivity to insulin. However, the deficient animals were found to be capable of secreting epinephrine, and the insulin sensitivity was probably not increased because of lack of this secretion.

Woodbury, Dixon M. (*Dept. of Pharmacol., Univ. of Utah Coll. of Med., Salt Lake City, Utah*): EXTRARENAL EFFECTS OF DESOXYCORTICOSTERONE, ADRENOCORTICAL EXTRACT AND ADRENOCORTICOTROPHIC HORMONE ON PLASMA AND TISSUE ELECTROLYTES IN FED AND FASTED RATS. Am. J. Physiol. *174*:1-19, July 1953.

The author studied the effect of desoxycorticosterone acetate (DCA), adrenocortical extract (ACE), and adrenocorticotrophic hormone (ACTH) on the distribution of electrolytes in the plasma and tissues of postcibal and fasted rats 24 hours after bilateral nephrectomy. It was concluded that these hormones influence electrolyte metabolism in every tissue of the body and that this influence is exerted independently of their known effects on the kidney.

Wright, Phyllis Mann; and Kochakian, Charles D. (*Depts. of Physiol. and Vital Econ. and Pediat., Univ. of Rochester, Rochester, N. Y.*): METABOLIC EFFECTS OF TESTOSTERONE PROPIONATE IN EXPERIMENTAL DIABETES. Am. J. Physiol. 173:217-22, May 1953.

The protein anabolic action of testosterone propionate occurs in the phlorizin and alloxan-diabetic rat in a manner similar to that observed in nondiabetic rats. The androgen does not detectably ameliorate the glucosuria.

Wylie, Mary E. S. (*Dept. Child Health, Univ. of Glasgow, and the Royal Hosp. for Sick Children, Glasgow, Scotland*): A CASE OF CONGENITAL DIABETES. Arch. Dis. Childhood, 28:297-99, August 1953.

Seven cases of diabetes mellitus with the onset in the neonatal period are reviewed. A patient diagnosed at 17 days, treated with insulin, and thriving at 8 months is described.

Zierler, K. L.; Folk, B. P.; and Lilienthal, J. L., Jr. (*Depts. of Med. and of Environmental Med., The Johns Hopkins Univ. and Hosp., Baltimore, Md.*): ON THE MECHANISM OF ACTION OF A-TOCOPHERYL PHOSPHATE, WITH SPECIAL REFERENCE TO CARBOHYDRATE METABOLISM OF STRIATED MUSCLE: I. MODIFICATION OF EPINEPHRINE EFFECT (HYPERLACTACIDEMIA) BY A-TOCOPHERYL PHOSPHATE IN THE RAT. Bull. John Hopkins Hosp. 92:26-31, January 1953.

In rats pretreated with a-tocopheryl phosphate, administration of epinephrine failed to provoke the degree of hyperlactacidemia produced ordinarily in response to epinephrine. It is concluded that a-TPh suppresses glycogenolysis in skeletal muscle.

Zierler, K. L.; Levy, R. I.; and Lilienthal, J. L., Jr. (*Depts. of Med. and of Environmental Med., The Johns Hopkins Univ. and Hosp., Baltimore, Md.*): ON THE MECHANISM OF ACTION OF A-TOCOPHERYL PHOSPHATE, WITH SPECIAL REFERENCE TO CARBOHYDRATE METABOLISM OF STRIATED MUSCLE: III. INHIBITION OF INSULIN-INDUCED GLYCOGENESIS IN ISOLATED RAT DIAPHRAGM. Bull. Johns Hopkins Hosp. 92:41-46, January 1953.

When a-tocopheryl phosphate (a-TPh) was administered to rats and the isolated diaphragm was subsequently incubated in a medium containing insulin and glucose, it was found that, whereas glucose uptake and oxygen consumption were unaffected by administration of a-TPh, the accumulation of glycogen in the tissue was significantly less than in the normal. These data support previous experiments interpreted to indicate that a-TPh inhibited carbohydrate metabolism in skeletal muscle at the level of the phosphoglucomutase step.

Zierler, K. L.; Levy, R. I.; and Andres, R. (*Depts. of Med. and of Environmental Med., The Johns Hopkins Univ. and Hosp., Baltimore, Md.*): DISSIMILATION OF GLUCOSE-1-PHOSPHATE AND OF FRUCTOSE-1,6-PHOSPHATE BY ISOLATED RAT DIAPHRAGM AND BY CELL-FREE EFFLUENT FROM RAT DIAPHRAGM. Bull. Johns Hopkins Hosp. 92:7-25, January 1953.

Segments of diaphragm and intact anterior gracilis muscle from normal rats were capable of dissimilating glucose-1-phosphate or fructose-1,6-phosphate added in vitro, despite the fact that these molecules have been considered not to penetrate the cell. Glycolysis occurred because an entire glycolytic enzyme system was transferred from the diaphragm to the extracellular phase under circumstances similar to those in which rat diaphragm has been employed as a tool for the study of carbohydrate metabolism. Dissimilation of hexose phosphate substrates, even in the presence of muscle tissue, occurred largely, if not entirely, in the medium and not in the cells. Incidental to this study were observations suggesting that isolated rat diaphragm was capable of replenishing its glycolytic enzymes.

Zieve, Leslie; and Hill, Earl (*V. A. Hosp., Minneapolis, and Univ. of Minnesota, Minneapolis, Minn.*): PROGNOSIS IN MODERATE OR SEVERE DIABETIC ACIDOSIS. A.M.A. Arch. Int. Med. 92:63-74, July 1953.

Factors of prognostic importance in moderate or severe diabetic acidosis have been evaluated with respect to their effectiveness in discriminating between patients who survive and patients who die of acidosis. The independently significant factors have been combined in a weighted formula yielding a single score representing the over-all severity of the acidosis with optimal effectiveness. Considered individually the order of effectiveness of the significant prognostic variables was age, blood pressure, associated condition, blood urea nitrogen, degree of unconsciousness and duration of coma. Blood

sugar and carbon dioxide combining power did not significantly differentiate between the two groups. When considered simultaneously, with allowances for their interdependence, the measurements may be regrouped into the following three levels of significance: highest—associated condition, blood sugar and blood urea nitrogen; intermediate—blood pressure and duration of coma; and lowest—degree of unconsciousness. Age had no independent contribution, and carbon dioxide combining power remained insignificant. For a given degree of severity, a high blood sugar was observed to be a favorable prognostic sign. The severity score, representing an optimal linear combination of the independently significant variables, was three times as effective as the prognostic factors considered individually and one and one half times as effective as any of the previously suggested methods for combining the factors. A simplified tabulation is presented enabling ready application of the formula in practice.

Zieve, Leslie; and Hill, Earl (*V. A. Hosp., Minneapolis, and Univ. of Minnesota, Minneapolis, Minn.*): DESCRIPTIVE CHARACTERISTICS OF A GROUP OF PATIENTS WITH MODERATE OR SEVERE DIABETIC ACIDOSIS. A.M.A. Arch. Int. Med. 92:51-62, July 1953.

Of 124 patients, 71 per cent recovered and 29 per cent died in acidosis. Those who died were, on the average, two decades older. They were also more obese and had higher blood pressures. More of them had no previous knowledge of their diabetes and did not take insulin, and fewer of them had previous episodes of acidosis. They were in acidosis longer before hospitalization, and twice as many, proportionately, were unconscious on admission. Only two-thirds of either group had vomiting as a symptom, and very few had bloody or coffee-ground vomitus. Body temperature was lower and respiratory rate higher among those whose outcome was fatal. One-third of them were in shock on admission and three-fifths likewise at some time during the first six hours. One-half of those who died and one-tenth of those who lived had a moderate or severe complicating condition. Oliguria or anuria was present on admission in one-half of the patients who died and in one-twentieth of the surviving patients. The degree of hyperglycemia was slightly greater among the patients who died. There was no difference between the groups in the level of the carbon dioxide combining power. Azotemia was much more frequent on admission among the patients who died. Two-fifths of the latter had no diacetic acid in their urine. All but a few of either group had acetonuria.

Those who lived and those who died received essentially the same treatment during the critical first three hours after admission. Thereafter the tendency was to increase slightly the vigorousness with which the more severely ill patients were treated. The patients who recovered received parenterally an average of 216 units of insulin, 4.2 liters of fluid, 27 gm. of sodium chloride, 15 gm. of sodium, 90 gm. of dextrose, and 16 gm. of alkali in 24 hours. The patients who died received parenterally an average of 252 units of insulin, 6.5 liters of fluid, 39 gm. of sodium chloride, 19 gm. of sodium, 108 gm. of dextrose, and 16 gm. of alkali in 24 hours. The rapidity of recovery from acidosis was highly variable. An average of 21 hours elapsed before the surviving patients recovered fully. Likewise, an average of 21 hours elapsed before death occurred in the patients who died. Sixty per cent of the survivors responded to questions on admission. Seventy per cent of the patients who died failed to respond at the time of admission. In the group of patients who recovered, the blood sugar returned to normal, on the average, in 17 hours, the carbon dioxide combining power in 24 hours, and the blood urea nitrogen in 38 hours. The urine acetone disappeared in 36 hours. The first two of these determinations were normal before death in 29 per cent of the patients who died; the third was normal in 11 per cent.

EDITORIALS

The Charles H. Best Institute

The dedication of The Charles H. Best Institute at the University of Toronto in September was an event of major importance in the scientific world. It is natural for the readers of this Journal to be especially interested because of the discovery of insulin in this location, because of the research concerning diabetes and related problems which have been carried on since then under the leadership of one of the partners in this epoch-making discovery and because of the promise of progress in this field which can be expected in the future with the facilities which are now available in the new Institute. The members of the American Diabetes Association also have a strong personal interest in honors bestowed on the former president of the Association whose name appears on the building. For this reason, it is gratifying to present in the Journal a record of the proceedings as well as the speeches made at the meetings held at the time of the opening of The Institute.

The program began in the afternoon of September 15, with a special convocation at which the University of Toronto conferred honorary degrees on five scientists and physicians of world-wide reputation. Addresses were delivered by two distinguished guests, Sir Lionel Whitby and Sir Henry Dale. The official opening of The Institute then took place. At this time Professor Best was presented with a portrait of himself which now hangs in the hall of the building.

In the evening, members of the faculty and their many guests were entertained by the University at a Banquet in the Great Hall of Hart House. Among the guests who had come from various parts of Canada, the United States, Europe and South America were three winners of the Nobel Prize, (Dale, Houssay and Adrian) and three holders of the Order of Merit, (Dale, Adrian and Penfield), the highest distinction held by a total of 24 in the British Empire.

On the second day, the first scientific program was presented at The Institute. Papers were read by Prof. Joseph P. Hoet, Louvain, Belgium and R. D. Lawrence, London, England. Professor Best submitted to distinguished scientists who were present the following question: Which of your scientific investigations has given you the most satisfaction and pleasure? Replies were given by Prof. E. D. Adrian, President of the Royal Society of London, Sir Henry Dale, past President of the Royal Society, Dr. Bernardo A. Houssay, Nobel Prize winner in medicine, Buenos Aires; Dr. Elliott P. Joslin, Boston, Honorary President, American Diabetes Association; Dr. Wilder Graves Penfield, Director of the Neurological Institute, McGill University, Montreal and Sir Lionel Whitby, Vice-Chancellor, University of Cambridge. The information contained in the replies gives an indication of the variety of methods by which scientific progress may be achieved.

The Charles H. Best Institute will be the home of teaching and research in physiology at the University of Toronto. It will provide increased accommodations and facilities for both the Department of Physiology and the Banting and Best Department of Medical Research. Its influence will be felt far beyond the limits of the University and the city. Students trained as undergraduates and graduates by Professor Best and his associates will be enriched by the scientific viewpoint derived from this experience as they leave to carry on their careers in the practice of medicine, in teaching and in laboratory investigation throughout Canada and other parts of the world.

THE DEGENERATIVE COMPLICATIONS OF DIABETES

CURRENT CONCEPTS OF PATHOGENESIS

The specific lesions of the retina and the renal glomerulus mark diabetic vascular disease as something apart from all other varieties. In searching for its cause, we must look further than investigators who are trying to discover why so many middle-aged Americans without diabetes die every year of coronary disease. The diabetic too is subject to coronary atherosclerosis, and perhaps for the same reasons, but it seems more likely that the key to his vascular problem lies in finding the cause of the capillary lesions of the eye and kidney to which he is almost uniquely susceptible.

One of the major questions is whether such disorders of the blood vessels are the result of hereditary or constitutional influences, transmitted along with the tendency toward diabetes, or whether they are the result of diabetes itself. The great majority of vascular abnormalities appear only after 10 to 20 years of diabetes. Therefore, the occasional finding of retinopathy at the time, or shortly after, glycosuria is first discovered suggests that some factor beside or in addition to diabetes was responsible. The observation loses some significance when it is realized how difficult it is to place precisely the actual onset of diabetes in such cases. The fact is that the question of genetic and allied factors is one on which we have no direct evidence.

On the other hand, it has been established in both man and animals that premature vascular disease occurs in the presence of diabetes alone under conditions which almost certainly exclude inherited or constitutional influences. Lawrence[1] refers to such lesions in patients with diabetes produced by disease, such as hemochromatosis and chronic relapsing pancreatitis. Degeneration of the aorta[2] and coronary arteries[3] has been observed in the experimental diabetes of dogs, and lesions resembling intercapillary glomerulosclerosis have been reported in pituitary diabetic dogs[4,5] and in partially pancreatectomized[6] as well as alloxanized[7] diabetic rats. The implication of these observations is reinforced by the fact that the incidence of degenerative disorders is more closely related to the duration of diabetes than to any other element of the disease, suggesting, again, that there is something about diabetes itself which, acting over a long period of time, leads to damage of the blood vessels.

SIGNIFICANCE OF SERUM LIPIDS

What this something is has not been determined. It is currently the fashion to regard the serum lipids as the number one enemy of the arteries. In both diabetics and nondiabetics it has been shown repeatedly that there is some overall *association* between high levels of cholesterol and the presence of atherosclerosis. There are, however, several points to be borne in mind. First, there are many cases in which there is no such correlation. Second, association is not synonymous with cause. Third, hypercholesterolemia in the *treated* diabetic is neither so common nor so marked as many have supposed. Fourth, despite the production of atherosclerosis in five species of animals by methods involving cholesterol feeding, no one has reported retinal lesions. Perhaps they have not been sufficiently looked for. I can only say that I have searched for them in vain, in cholesterolized rabbits which later showed severe atherosclerosis at autopsy, and in a number of Dr. Forest Kendall's atherosclerotic dogs with serum cholesterol levels maintained for many months in the neighborhood of 1000 mg. per cent by cholesterol and thiouracil feeding.[8] It should not require emphasis that, until someone succeeds in producing retinal and glomerular lesions as well as atherosclerosis in experimental animals, the complete picture of diabetic vascular disease cannot be said to have been duplicated.

LIPOPROTEINS

Studies of the lipoproteins have closely resembled those of cholesterol in showing a general but decidedly inconstant relationship in both diabetics and nondiabetics between blood levels and the incidence of atherosclerosis. Here, too, it has not been possible to demonstrate that this relationship represents cause and effect. Keiding[9] and his colleagues have reported elevated concentrations of serum lipoproteins in patients with diabetic retinopathy, but it is not stated whether these patients also had intercapillary glomerulosclerosis, and since serum lipids tend to be high in this syndrome as well as in nephritis of other origins, it is difficult to evaluate the significance of their observation.

FATTY ACIDS

The recent investigations of Hirsch, Phibbs and Carbonaro[10] are perhaps the most interesting of any in the field of lipids. Studying especially the esterified fatty acids of the blood in diabetic patients, they have found that these substances, unlike cholesterol and the lipo-

Presented at the Postgraduate Course given by the American Diabetes Association in Rochester, Minnesota, January 19-21, 1954.

proteins, increase rather sharply after a fat meal, that such increases are appreciably greater when the blood sugar is high than when it is normal, and that even the fasting levels of the esterified fatty acids, when determined day after day, go up and down in parallel with the blood glucose. For those who believe that atherosclerosis is caused by disturbances in fat metabolism, and that control of the blood sugar is the way to prevent it, here is an experiment that ties both ideas together into a neat and tempting package. The trouble is that no one has proved that hyperlipemia causes atherosclerosis in man. If this is ever established, the work of Hirsch and his colleagues will represent a contribution of major importance, although its relation to the capillary lesions of diabetes remains obscure.

BLOOD SUGAR

This brings us to the subject of hyperglycemia. That an excess of circulating glucose alone is injurious to blood vessels has not been seriously entertained by most investigators, although it must be admitted that definite proof is lacking. The possibility exists, however, that some substance associated with high glucose levels may be pathogenic. Perhaps the esterified fatty acids are one example. It may be that another is the mucopolysaccharides of the blood. Much interest attaches to these compounds today, for they have been found in both the microaneurysms of the retina [11] and the glomerulus of the Kimmelstiel-Wilson kidney,[12] a fact which, together with certain similarities in structure, more than hints at a common pathogenesis. It has been suggested, indeed, that lesions of the capillaries and smaller arteries may occur in other places where they have been difficult to demonstrate by ordinary technics, and that they may be the primary manifestation of vascular disease. Ditzel,[13] for example, utilizing microscopic examination of the brilliantly illuminated conjunctiva, has reported abnormalities of the capillaries and venules in diabetic patients and even in their children. Megibow and his associates [14] have shown by microplethysmographic methods that there is impairment of circulation in the toes of some diabetics in whom available methods fail to show disease of the more proximal arteries. Vasospastic influences were excluded by the use of tetraethylammonium. Since these studies were carried out in living patients, it was not possible to confirm the integrity of the larger vessels by histologic means.

GLUCOSAMINE

Returning to the mucopolysaccharides, it should be said for purposes of orientation that this term is applied to such substances as chondroitin sulfate (a component of cartilage), mucoin sulfate, hyaluronic acid (the intercellular cement substance) and heparin. Chemically, a mucopolysaccharide is a polysaccharide containing a hexosamine. One of the hexosamines is glucosamine. Glucosamine, which is present in the blood in a protein-bound polysaccharide, can be measured by chemical means, thus providing some estimate of the concentration of serum polysaccharides. It must be stated that the methods for determining this substance are rather tricky and possess a somewhat uncertain degree of specificity although they do yield fairly reproducible results.

In 1948 Jacobs [15] reported that the blood glucosamine levels were higher in diabetic than in nondiabetic individuals, and further that among the diabetics they varied directly with the blood sugar. In 1953 Berkman and associates[16], although failing to confirm this relationship, found elevated levels of protein-bound polysaccharides and glucosamine in the blood of diabetics with degenerative vascular disease compared with diabetics without such complications. The presence of mucopolysaccharides in the specific histologic lesions of the diabetic makes this finding one of unusual interest. Enthusiasm, however, must be tempered, as the authors are careful to point out, by the knowledge that concentrations of blood glucosamine are increased in a number of disorders manifested by tissue destruction and repair—processes which surely take place over many square centimeters of intima in advanced arteriosclerosis. Thus it is possible that hyperglucosaminemia may be a result rather than a cause of vascular disease. At any rate these investigations provide us with a new perspective in the search for the cause of the mysterious capillary lesions of the eye and kidney.

PITUITARY AND ADRENALS

This search has been given fresh impetus by the finding of Becker[17] of capillary aneurysms and Kimmelstiel-Wilson lesions in alloxan diabetic rabbits treated with corticotropin. Attempts to produce the lesions with alloxan alone have been unsuccessful. Rabbits treated with cortisone or Compound F alone showed the glomerular changes but not the retinal. Becker's working hypothesis is that both insulin deficiency and adrenocortical overactivity are factors in the development of these lesions. This hypothesis receives some support from a few clinical observations. Two cases are reported by Lawrence[18] and three by Becker[17] in which retinopathy first appeared or became much worse during

pregnancy and subsided after delivery. Rich[19] refers to the finding at autopsy of lesions of the Kimmelstiel-Wilson type in a nondiabetic patient treated for a prolonged period with corticotropin. Poulsen[20] has described a case of well established diabetic retinopathy from which the patient recovered following the onset of Simmond's disease.

Studies of the retina in patients with acromegaly and diabetes and with Cushing's syndrome and diabetes might be expected to shed some light on this subject. Several years ago, the records of a number of such cases were reviewed with somewhat disappointing results.[21] Of 16 patients with acromegaly, three had diabetes, and of these, two had diabetic retinopathy. Among 10 patients with Cushing's syndrome there were seven with diabetes or impairment of glucose tolerance; of these only one had retinopathy and this was of the hypertensive, not the diabetic, type. A larger number of these important cases must be studied before we can come to any conclusions regarding the relationship of the anterior pituitary and the adrenal cortex to the renal and retinal lesions of diabetic patients.

CONCLUSION

Thus, we must end this discussion, as we have ended all others like it, with the conclusion that, despite encouraging advances, the cause of degenerative vascular disease in diabetes remains unknown. Until it is known, it seems but the part of wisdom to employ against this destroyer of blood vessels the only weapon we possess, imperfect as it is—the careful control of blood sugar.

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Organization Section

Next Annual Meeting

Members and others interested in diabetes are urged to make arrangements now to attend the Fourteenth Annual Meeting which will be held in San Francisco, June 19 and 20. The meeting, as in the past, will immediately precede the Annual Session of the American Medical Association which this year is scheduled for June 21-25.

Henry T. Ricketts, M.D., Chairman of the Association's Committee on Scientific Programs, reports that some excellent material already has been received for the Scientific Sessions and again issues an invitation to physicians and other scientists to submit abstracts of papers which they would like to present. In order to facilitate review by the Committee, seven copies of an abstract of each proposed paper should be submitted. Abstracts should not exceed 300 words in length.

The joint meeting with The Endocrine Society will be held, as customary, on the first day of the Annual Meeting, and plans now are being made for the session to be conducted in the Fairmont Hotel, Saturday afternoon, June 19. Sir Henry Hallett Dale, eminent British physiologist, will come to the United States especially to deliver the Banting Memorial Lecture sponsored by the American Diabetes Association at the joint session with The Endocrine Society on Saturday afternoon, June 19. Sir Henry has been the recipient of many honors in the field of medicine and physiology, including a share of the Nobel Prize for Medicine in 1936. He is currently chairman of the Wellcome Trust, London.

The Fairmont Hotel has been selected as headquarters for the American Diabetes Association. However, because of restrictions imposed by other organizations, it has been impossible for the Association to secure a block of rooms there for its members. Reservations for accommodations in this and other hotels should be made through the Housing Bureau of the American Medical Association. Information concerning hotel accommodations is currently being published in *The Journal of the American Medical Association.*

Arrangements are being made to hold the Banquet on Saturday evening, June 19, in the Fairmont Hotel. Dinner tickets are available at $6.00 each and may be secured from the national office prior to June 4. In view of its success last year, another social hour will be held preceding the Banquet. Members, their families and friends are cordially invited to attend both the social hour and the Banquet.

Funds from the American Diabetes Association Available for Research

As announced for the first time in the last issue of DIABETES, two fellowships of approximately $2,500 each are available this academic year for adequately trained investigators who will give their full time to a problem in the general field of diabetes in the laboratory or clinic of a recognized authority on this subject. Applications should be sent to the Executive Director, the American Diabetes Association, 11 West 42nd Street, New York 36, N.Y.

New Exhibits

The Council has authorized two new exhibits, one for the medical profession and the other for laymen. Dr. William R. Kirtley, Chairman of the Committee on Scientific Exhibits, reports that the Committee is planning one on "Management of Diabetes." It is anticipated that the exhibit will be ready for display at the 1954 Annual Session of the American Medical Association in San Francisco.

The Committee on Scientific Exhibits also is responsible, along with the Committees on Detection and Education, and Information for Diabetics, chaired by Drs. John A. Reed and Alexander Marble, respectively, for a lay exhibit. This will be directed to the general public and not to diabetics. The display should be ready for Diabetes Week next fall, if not before.

Change in Deadline for Essay Contest

The closing date for the Essay Contest has been changed from April 1 to May 15, 1954. The contest is open to medical students and physicians who have been out of medical school for no more than two years.

Members of the Association and subscribers to DIABETES are again urged to remind their students and young colleagues to submit their papers by that date.

Candidates may choose any subject relating to diabetes. The length of the paper may be from six to eighteen pages, typewritten and double-spaced. Manuscripts should be sent to the Editorial Office of DIABETES, 11 West 42nd Street, New York 36, N.Y. The papers will be reviewed by the Editorial Board which, in selecting the best paper, will take into consideration the value of the material and the method of presentation. The prize of $250 is made possible again through the kindness of the St. Louis Diabetes Association.

Request for 1953 Drive Reports

The Chairman of the Committee on Detection and Education, Dr. John A. Reed, has requested that all Chairmen of Committees on Diabetes of County and State Medical Societies, and Chairmen of Committees on Detection and Education of Affiliate Associations, submit their 1953 reports as soon as possible.

From the reports received to date it appears that the 1953 Drive was highly successful. A summary undoubtedly will be published in a future issue of DIABETES.

New Members

The following Active Members were elected as of January 1 and February 1, 1954:

Delaware
Aitken, Douglas H. — Wilmington

Florida
Austin, George C. — Miami

Georgia
Paullin, William L., Jr. — Atlanta

Illinois
Campione, N. Louis — Chicago
Garrett, Sherman S. — Champaign
Greeley, Harry Y. — Aurora
Manelli, Louis A. — Chicago

Kansas
Crary, John E. — Topeka
O'Donnell, Leonard A. — Wichita

Massachusetts
Beigelman, Paul M. — Boston
Colombo, N. John — Hudson

Minnesota
Breidahl, Harald D. — Rochester

New Jersey
Leevy, Carroll M. — Jersey City

New York
Glenn, Morton B. — New York
Krieger, Jacob — Brooklyn
Krzywicki, Stanley T. — Syracuse
McDermott, Kenneth J. — Syracuse
Quigley, Thomas J. — Staten Island
Schultz, Louis A. — Bronx
Weinstein, Joseph — Bronx
Zodikoff, Meyer — Newburgh

Ohio
Boehm, Lloyd A. — Toledo
Pollack, Alexander — Columbus

Oklahoma
Hendren, Scott — Oklahoma City

Pennsylvania
Berenbaum, A. A. — Philadelphia
Davis, Norman — Pittsburgh
Frank, Mary E. — Philadelphia
Mateer, Frank M. — Pittsburgh
Snydman, Leonard — Philadelphia

Tennessee
Crowder, William C. — Maryville

OTHER COUNTRIES

Puerto Rico
Mattei, Tito — Yauco

Italy
Andreani, D. V. — Pisa

News Notes

The Clinical Meeting, American Medical Association, St. Louis, December 1-4, 1953

The subject of diabetes was well represented in the scientific portion of the meeting. The major contribution was an extensive exhibit entitled "Diabetes Today" by Drs. Howard F. Root, Elliott P. Joslin, Priscilla White, Alexander Marble, Allen P. Joslin and Leo Krall of the Joslin Clinic, Boston. The exhibit was supplemented by a Question and Answer Conference held in an adjoining room. The entire program was under the direction of the Joslin Clinic, New England Deaconess Hospital, Boston, and the St. Louis Diabetes Association. Doctor Root served as Chairman.

Members of the American Diabetes Association who participated in the Conference, which was scheduled from December 1 to noon on December 4, were: Joseph C. Edwards, M.D.; John L. Kennedy, M.D.; William H. Olmsted, M.D.; Henry E. Oppenheimer, M.D.; Harold K. Roberts, M.D.; Howard F. Root, M.D.; E. Paul Sheridan, M.D.; and Priscilla White, M.D.

Among the Association members who took part in the scientific section were: Geza de Takats, M.D., Chicago, and John B. McKittrick, M.D., Boston, Mass., who discussed "Surgical Management of Peripheral Arterial Deficiencies," on Thursday afternoon, December 3.

Research Fellowship Established in Honor of Doctor Wilder

The establishment of a Fellowship for post-doctorate training in the science of nutrition was announced recently by The National Vitamin Foundation. The fellowship will be known as the Russell M. Wilder Fellowship, honoring Russell M. Wilder, M.D., a past President of the American Diabetes Association.

The Fellowship will be part of the program of The National Vitamin Foundation, designed to stimulate the training of qualified young men and women for pursuing research and teaching in the science of nutrition. The Foundation, established in 1946, functions primarily through distribution of grants-in-aid to universities, colleges and other qualified research institutions and individuals, for research and clinical studies and training of qualified investigators. Its objective is to improve the health and welfare of mankind through better nutrition and to initiate and encourage research relating to medicine and health.

Candidates for the Fellowship must apply in writing to The National Vitamin Foundation, 15 East 58th Street, New York 22, N. Y. To be eligible for the three-year $15,000 Fellowship, candidates must hold a doctor's degree in medicine or in one of the basic sciences, biology, physiology, chemistry, or biochemistry. Application must be made on or before March 15th. Notification of the action taken by the Foundation's Scientific Advisory Committee on the application will be sent to all applicants before July 1, 1954, and the Fellowship will become effective for the successful applicant at the beginning of the academic year in September 1954.

Doctor Wilder, who at present is residing in Rochester, Minnesota, served as head of the Department of Medicine, Mayo Foundation, in the years 1931 through 1950. Later, he became Director of the National Institute for Arthritis and Metabolic Diseases of the National Institutes of Health, recently retiring from that position.

Doctor Joslin

The admitting office of the New England Deaconess Hospital received a telephone call from Elliott P. Joslin, M.D., at 9:30 p.m., Tuesday, October 26. The hospital was informed by Dr. Joslin that he wished to have a bed reserved and that he was being admitted for removal of an appendix. He arrived at the hospital by taxi, unaccompanied, and the resident who saw him confirmed his diagnosis. Later that night a "red hot appendix" was taken out.

The following morning Dr. Joslin called his secretary and kept her busy with dictation until noon. In the afternoon, he stated he would see his patients, but was persuaded to let his associates take his appointments. On November 3 he left the hospital and on the way home stopped at the polling station to cast his vote. On November 6, eleven days after the operation, he came from his home to the hospital to give his regular Friday morning lecture to patients.

Doctor Joslin deserves congratulations for his rapid recovery and also for the accuracy of his self-diagnosis of appendicitis.

Research Grants

A total of 651 medical research grants, aggregating $6,428,435, was approved in December by the Public Health Service. The approval was made on recommendations by advisory councils to the National Institutes of Health.

Of 98 projects with a total of $1,003,116, the National Institute of Arthritis and Metabolic Diseases recommended approval of 67 projects adding up to $606,031. The Institute also has announced that it is making available a limited supply of radioactive corticosterone (Compound B) to investigators, without charge. Information is obtainable from Endocrinology Study Section, National Institutes of Health, Bethesda 14, Md.

Binders for Volume 3 of DIABETES

A binder for 1954 matching those for Volumes 1 and 2 (1952-53 issues) of DIABETES is now available for immediate shipment at a price of $2.00. This insert binder is sturdy and attractive and will hold six issues. Readers are urged to purchase theirs before present stocks are depleted. Binders for Volumes 1 and 2 also are available at the same price.

Personal

Four members of the American Diabetes Association participated in the Medical Symposium held as part of the Dedication Exercises at the Samuel P. Capen Hall, University of Buffalo Schools of Medicine and Dentistry, on December 12. Doctor Charles H. Best of Toronto presided and the following took part in the Symposium: Jerome W. Conn, M.D., Ann Arbor, Michigan, "Metabolic Consequences of Stress in Man;" Thaddeus S. Danowski, M.D., Pittsburgh, "Parameters of Electrolyte Needs During Parenteral Nutrition;" Herbert Pollack, M.D., New York City, "Amino Acids in Parenteral Nutrition."

At the meeting of the Council of the American Diabetes Association, held in Rochester, Minnesota recently, Russell M. Wilder, M.D., was elected to honorary membership in the Association. Doctor Wilder was one of the members of the Council when the Association was founded and served as President, 1946-1947. The recent action of the Council gave recognition to his lifetime work in the field of diabetes, including practice and research, in addition to his services to the Association.

Obituaries

DANIEL B. MARCUS, M.D., of Detroit, a member of the American Diabetes Association since 1941, died on September 26 at the age of 45. He had headed the diabetic service for many years at Grace Hospital in Detroit.

After receiving his medical degree from the Detroit College of Medicine and Surgery in 1931, Doctor Marcus interned at Grace Hospital and began the practice of medicine in 1933. Motivated by the teaching of the late Dr. L. F. G. Wendt, Doctor Marcus became greatly interested in diabetes even as an intern and during his entire medical career he restricted his work to treating this disease and its complications. In this connection, he taught numerous groups of interns and residents as well as many classes of student nurses, emphasizing the importance of good control of diabetes.

Besides operating the diabetic clinic at Grace Hospital, he was active in the medical management of the former Grace Hospital Diabetic Camp. He had few hobbies, although from time to time he would make fishing trips with close acquaintances.

HENRY THOMAS FOLEY, II, M.D., of Pittsburgh, died last fall at the age of 48.

An Active Member of the American Diabetes Association since 1949, Doctor Foley also was a member of the Pittsburgh Diabetes Association. He was a graduate of the University of Pittsburgh School of Medicine and held a position there as Instructor of Internal Medicine. He was also Associate Staff Physician at the Presbyterian and Woman's Hospital of the University of Pittsburgh Medical Center. He was active in establishing cardiac evaluation clinics for workers in the industries of Pittsburgh.

Doctor Foley was certified by the American Board of Internal Medicine in 1949. He was a member of the Aero Medical Association and the American Heart Association.

KALMAN EISENBUD, M.D., an Active Member of the American Diabetes Association since 1941, died on January 19 in New York City after a long illness.

Born in Russia 72 years ago, Doctor Eisenbud received his medical degree from New York University Bellevue Medical College. He was attending physician at Riverside, Beth David, Jewish Memorial and Harlem Hospitals in New York. He also held a reserve commission as Senior Surgeon in the Public Health Service. His practice was limited to diseases of metabolism in recent years and he devoted nearly all of his attention to the care of diabetic patients. He was the author of articles on the importance of diabetes as a national health problem, medical care of the surgical diabetic, renal glycosuria and other related subjects.

Doctor Eisenbud is survived by his wife, a daughter, and two sons, one of whom is a physician, Dr. Leon Eisenbud of New York City.